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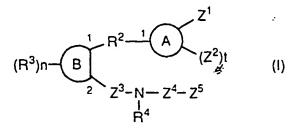
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- (54) SULFONAMIDE AND CARBOXAMIDE DERIVATIVES AND DRUGS CONTAINING THE SAME AS THE ACTIVE INGREDIENT
- (57) The sulfonamide or carboamide derivatives of the formula (I) and a pharmaceutical composition which comprise them as an active ingredient:



(wherein A ring, B ring is carbocyclic ring, heterocyclic ring; Z^1 is -COR 1 , -CH=CH-COR 1 etc.; Z^2 is H, alkyl etc.; Z^3 is single bond, alkylene; Z^4 is SO $_2$, CO; Z^5 is alkyl, phenyl, heterocyclic ring etc.; Z^2 is CONR 3 , O, S, NZ 6 , Z^7 -alkylene,

alkylene etc.; R³ is H, alkyl, halogen, CF₃ etc.; R⁴ is H, (substituted) alkyl etc.; n, t is 1-4).

The comp unds of the formula (I) can bind to receptors of PGE₂ and show antagonistic activity against the action thereof or agonistic activity. Therefore, they are considered to be useful as medicine for inhibition of uterine contraction, analgesics, antidiarrheals, sleep inducers, medicine for increase of vesical capacity or medicine for uterine contraction, cathartic, suppression of gastric acid secretion, antihypertensive or diuretic agents.

Description

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Field of technology

[0001] This invention relates to sulfonamide and carboamide derivatives. More particularly, this invention relates to

(1) the compounds of the formula (I)

$$(R^{3})n - B = Z^{3} - N - Z^{4} - Z^{5}$$

$$(R^{3})n - B = Z^{3} - N - Z^{4} - Z^{5}$$

$$(R^{3})n - B = Z^{3} - N - Z^{4} - Z^{5}$$

(wherein all symbols are as hereinafter defined.),

(2) processes for preparing them and

(3) Prostaglandin E2 (abbreviated as PGE2) antagonists or agonists which comprise them as an active ingredient.

Background

[0002] PGE_2 has been known as metabolite in the arachidonate cascade. It has been known that PGE_2 causes uterine contraction, induction of pain, promotion of digestive peristalsis, awakening effect, vesica contraction, suppression of gastric acid secretion or reduction of blood pressure etc. The PGE_2 antagonist or PGE_2 agonist is expected to show the following actions.

[0003] To antagonize against PGE₂ means to suppress the effects above mentioned, so such an activity is linked to inhibition of uterine contraction, analgesic action, inhibition of digestive peristalsis, induction of sleep or increase of vesical capacity. Therefore, PGE₂ antagonists are considered to be useful for the prevention of abortion, as analgesics, as antidiarrheals, as sleep inducers or as agents for treating pollakiuria.

[0004] To show PGE₂ agonistic activity means to promote the effects above mentioned, so such an activity is linked to uterine contraction, promotion of digestive peristalsis, suppression of gastric acid secretion or reduction of blood pressure or diuresis. Therefore, PGE₂ agonists are considered to be useful as abortifacient, cathartic, antiulcer, antigastritis, antihypertensive or diuretic agents.

[0005] A lot of PGE₂ agonists including PGE₂ itself etc. have been known, but only a few compounds (PGE₂ antagonists) possessing the inhibition of activity of PGE₂ by antagonizing against PGE₂ have been known.

40 [0006] For example, the patent applications relating to PGE antagonists are as follows:

[0007] In the specification of WO-96/03380, it is disclosed that the compounds of the formula (A)

(wherein A is phenyl which may be substituted etc., B is ring system which may be substituted, D is ring system which may be substituted, R^{1A} is carboxyl etc., R^{2A} is H, C1-6 alkyl etc., R^{3A} is H, C1-4 alkyl, R^{4A} is H, C1-4 alkyl (as excerpt).) are active as PGE antagonists.

[0008] In the specification of WO-96/06822, it is disclosed that the compounds of the formula (B)

$$\begin{array}{c|c}
R^{3B} \\
CH^{-B} \\
R^{1B}
\end{array}$$
(B)

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(wherein A is ring system which may be substituted, B is hetero aryl ring which may be substituted or phenyl which may be substituted, D is ring system which may be substituted, X is (CHR⁴)_n or (CHR⁴)_pCR⁴=CR⁴ (CHR⁴)_q, R^{1B} is carboxyl etc., R^{3B} is H, C1-4 alkyl, R⁴ is H, C1-4 alkyl (as excerpt).) are active as PGE antagonists.

[0009] In the specification of WO-96/11902, it is disclosed that the compounds of the formula (C)

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(wherein A, B and D are various ring systems, R^{1C} is carboxyl etc., R^{3C} is H, C1-4 alkyl, Z is -(CH(R^5))_m etc. (as excerpt)) are active as PGE antagonists.

[0010] On the other hand, some compounds having a similar structure to the present invention compounds have been

[0011] For example, the following compound is described in Justus Liebigs Ann. Chem. (1909), 367, 133.

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(wherein RD is H or ethyl.)

[0012] The following compound is described in Khim. Geterotsild. Soedin (1974), (6), 760.

(F-1)

(wherein R^E is phenethyl, benzyl, hexadecyl, decyl, nonyl, butyl, propyl, ethyl, methyl.) [0013] The following compound is described in Khim. Geterotsikl. Soedin (1972), (10), 1341.

COOH

(wherein R^F is nitro or methoxy.) [0014] The following compound is described in Khim. Geterotsiki. Soedin (1972), (5), 616.

$$O_2N$$
 N
 N
 $COOH$
 O_2S
 Me
 Me

[0015] The following compound is described in Khim. Geterotsikl. Soedin (1976), (5), 641.

NH COOH
O2S
Me

[0016] The following compound is described in Khim. Geterotsiki. Soedin (1971), (7), 1028.

20 MeO NH COOH
O2S (J-1)

MeO NH COOH
O2S
Me

[0017] The following compound is described in Khim. Geterotsikl. Soedin (1970), (12), 1597.

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(wherein each RK is Br or Cl.)

[0018] The compounds of the formula (A), (B) and (C) in the related arts possess the same pharmacological activity as the present invention compounds. But there is a difference in structure as follows: The present invention compounds have sulfonamide or carboamide as an essential element in their structure. On the other hand, the compounds described in such related arts have either or alkylene in the corresponding part. So, it is not easy to predict the present invention compounds from the structure of these related arts.

[0019] In addition, the compounds of the formula (D) to (K) relate to the study for synthesis only. In these literature, there is no description on pharmacological activity. The carboxyl group in such compounds is connected at the ortho position, so the present invention compounds are different from such compounds in structure. Therefore, it is not easy to predict the present invention from such compounds possessing the different activity and structure.

The Disclosure of the Invention

40 [0020] The present invention relates to

(1) sulfonamide or carboamide derivatives of the formula (I)

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$$(R^{3})n - B = Z^{1} - Z^{1}$$

$$(Z^{2})t = Z^{3} - N - Z^{4} - Z^{5}$$

$$R^{4}$$
(I)

(wherein

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5 and 10 each, independently, is C5-15 carbocyclic ring or 5-7 membered heterocyclic ring containing one or two oxygen, sulfur or nitrogen atom(s), 15 Z¹ is -COR1, -C1-4 alkylene-COR1, 20 -CH=CH-COR1. -C=COR¹, or -O-C1-3 alkylene-COR1 (wherein R1 is hydroxy, C1-4 alkoxy or formula 25 NR⁶R⁷ (wherein R⁶ and R⁷ each, independently, is H or C1-4 alkyl.).), or -C1-5 alkylene-OH, 30 Z² is H, C1-4 alkyl, C1-4 alkoxy, nitro, halogen, trifluoromethyl, trifluoromethoxy, hydroxy or COR¹ (wherein R¹ is as hereinbefore defined.), Z³ is single bond or C1-4 alkylene. Z^4 is SO_2 or CO, Z⁵ is 35 (1) C1-8 alkyl, C2-8 alkenyl, or C2-8 alkynyl, (2) phenyl, C3-7 cycloalkyl, or 5-7 membered heterocyclic ring containing one or two oxygen, sulfur or nitrogen atom(s), or (3) C1-4 alkyl, C2-4 alkenyl or C2-4 alkynyl substituted by phenyl or C3-7 cycloalkyl 40 (phenyl, C3-7 cycloalkyl, and 5-7 membered heterocyclic ring containing one or two oxygen, sulfur or nitrogen atom(s) mentioned in the above (2) and (3) may be substituted by 1-5 of R5 (wherein R5 (if two or more R5, each independently) is H, C1-6 alkyl, C1-6 alkoxy, C1-6 alkylthio, nitro, halogen, tifluoromethyl, trifluorometh-45 oxy or hydroxy.).), R² is CONR8. NR8CO, CONR8-C1-4 alkylene, 50 C1-4 alkylene-CONR8. NR8CO-C1-4 alkylene, C1-4 alkylene-NR8CO,

C1-3 alkylene-CONR⁸-C1-3 alkylene, or C1-3 alkylene-NR⁵CO-C1-3 alkylene

(wherein each R8 is H or C1-4 alkyl.),

(wherein Z⁶ is H or C1-4 alkyl.),

O, S, NZ6

Z7-C1-4 alkylene, C1-4 alkylene-Z7, or C1-3 alkylene-Z7-C1-3 alkylene (wherein each Z⁷ is O, S or NZ⁶ (wherein Z⁶ is as hereinbefore defined.).), 5 CO-C1-4 alkylene, C1-4 alkylene-CO, C1-3 alkylene-CO-C1-3 alkylene, C2-4 alkylene, C2-4 alkenylene, or 10 C2-4 alkynylene, R3 is H. C1-6 alkyl, C1-6 alkoxy, C1-6 alkytthio, nitro, halogen, trifluoromethyl, trifluoromethoxy, hydroxy or hydroxymethyl, 15 R⁴ is (1) H,(2) C1-8 alkyl, C2-8 alkenyl, or C2-8 alkynyl, (3) C1-6 alkyl substituted by one or two substituent(s) selected from the group consisting of COOZ8, CONZ⁹Z¹⁰, and OZ⁸, (wherein Z⁸, Z⁹ and Z¹⁰ each, independently, is H or C1-4 alkyl.) and C1-4 alkoxy-20 (4) C3-7 cycloalkyl, or (5) C1-4 alkyl, C2-4 alkenyl or C2-4 alkynyl substituted by phenyl or C3-7 cycloalkyl 25 (phenyl and C3-7 cycloalkyl mentioned in the above (4) and (5) may be substituted by 1-5 of R⁵ (wherein R⁵ is as hereinbefore defined.).), and n and t each, independently, is an integer of 1-4, with the proviso that (1) R² and Z³ should be connected at the 1- or 2- position of 30 , and (2) when 35 40 is a benzene ring and (Z^2) t is other than COR¹, Z^1 should be connected at the 3- or 4-position of the benzene ring.). or a non-toxic salt thereof. (2) processes for preparing them and (3) PGE₂ antagonists or agonists which comprise them as an active ingredient. Detailed Description of the Invention [0021] In the formula (I), C1-4 alkyl in Z⁵ and R⁴ and C1-4 alkyl represented by Z², Z⁶, Z⁸, Z⁹, Z¹⁰, R⁶, R⁷ and R⁸ means methyl, ethyl, propyl, butyl and isomer thereof. [0022] In the formula (I), C1-6 alkyl in R4 and C1-6 alkyl represented by R3 and R5 means methyl, ethyl, propyl, butyl, pentyl, hexyl and isomer thereof. [0023] In the formula (I), C1-8 alkyl represented by Z⁵ and R⁴ means methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl,

[0027] In the formula (I), C2-8 alkynyl represented by Z5 and R4 means C2-8 alkyl having 1-3 of triple bond and, for

[0024] In the formula (I), C2-4 alkenyl in Z⁵ and R⁴ means vinyl, propenyl, butenyl and isomer thereof.

[0026] In the formula (I), C2-4 alkynyl in Z⁵ and R⁴ means ethynyl, propynyl, butynyl and isomer thereof.

example, vinyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl etc. and isomer thereof.

55 [0025] In the formula (I), C2-8 alkenyl represented by Z⁵ and R⁴ means C2-8 alkyl having 1-3 of double bond and, for

octyl and isomer thereof.

example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl etc. and isomer thereof.

[0028] In the formula (I), C1-4 alkoxy in R^4 and C1-4 alkoxy represented by Z^2 and R^1 means methoxy, ethoxy, propoxy, butoxy and isomer thereof.

[0029] In the formula (I), C1-6 alkoxy represented by R³ and R⁵ means methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy and isomer thereof.

[0030] In the formula (I), C1-6 alkylthio represented by R³ and R⁵ means methylthio, ethylthio, propylthio, butylthio, pentylthio, hexylthio and isomer thereof.

[0031] In the formula (I), C1-3 alkylene in Z¹ and R² means methylene, ethylene, trimethylene and isomer thereof.

[0032] In the formula (I), C1-4 alkylene in Z^1 and R2 and C1-4 alkylene represented by Z^3 means methylene, ethylene, trimethylene, tetramethylene and isomer thereof.

[0033] In the formula (I), C1-5 alkylene in Z^1 means methylene, ethylene, trimethylene, tetramethylene and isomer thereof.

[0034] In the formula (I), C2-4 alkylene represented by R² means ethylene, trimethylene, tetramethylene and isomer thereof.

[0035] In the formula (I), C2-4 alkenylene represented by R² means vinylene, propenylene, butenylene and isomer thereof.

[0036] In the formula (I), C2-4 alkynylene represented by R² means ethynylene, propynylene, butynylene and isomer thereof.

[0037] In the formula (I), C3-7 cycloalkyl in \mathbb{Z}^5 and \mathbb{R}^4 and C3-7 cycloalkyl represented by \mathbb{Z}^5 and \mathbb{R}^4 means cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl.

[0038] In the formula (I), C5-15 carbocyclic ring represented by

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 $\left(\mathsf{A}\right)$

and

B

means mono-, bi- or tri-ring of C5-15 carbocyclic aryl, or partially or fully saturated ring thereof.

[0039] For example, C5-15 carbocyclic aryl includes benzene, pentalene, indene, naphthalene, azulene, fluorene, anthracene etc. Partially or fully saturated ring thereof includes the above mentioned ring which is partially or fully saturated.

[0040] As for C5-15 carbocyclic ring, preferably, mono- or bi-ring of C5-10 carbocyclic aryl and the mentioned C5-7 cycloalkyl is listed, and more preferably, benzene, naphthalene, cyclopentyl, cyclohexyl or cycloheptyl.

[0041] In the formula (I), 5-7 membered heterocyclic ring containing one or two oxygen, sulfur or nitrogen atom(s) represented by

(A), (B)

and Z⁵ means 5-7 membered heterocyclic aryl ring containing one or two oxygen, sulfur or nitrogen atom(s) or partially or fully saturated ring thereof.

[0042] 5-7 membered heterocyclic aryl ring containing one or two oxygen, sulfur or nitrogen atom(s) includes pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, furan, pyran, oxepine, oxazepine, thiophen, thiain (thiopyran), thiepine, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, oxadiazine, oxazepine, oxadiazole, thiadiazole, thiadiazole, thiadiazepine etc.

[0043] 5-7 membered heterocyclic aryl ring containing one or two oxygen, sulfur or nitrogen atom(s) which is partially or fully saturated includes pyrroline, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, piperidine, piperazine, tetrahydropyrimidine, tetrahydropyridazine, dihydrofuran, tetrahydropyran, tetrahydropyran, dihydrofuran, tetrahydropyran, tetrahyd

thiophen, tetrahydrothiophen, dihydrothiain (dihydrothiopyran), tetrahydrothiain (tetrahydrothiopyran), dihydroxazole, tetrahydroxazole, dihydr isoxazole, tetrahydroisoxazole, dihydrothiazole, tetrahydrothiazole, dihydroisothiazole, tetrahydroisothiazole, morpholine, thiomorpholine etc. [0044] In the formula (I), halogen represented by Z², R³ and R⁵ means chlorine, bromine, fluorine and iodine. [0045] In the formula (I), as for Z³ which represents single bond or C1-4 alkylene, preferably, single bond or methylene is listed and more preferably, single bond. [0046] In the formula (I), as for \mathbb{Z}^4 which represents SO_2 or CO, preferably SO_2 is listed. [0047] In the formula (I), as for R4, preferably, every group is listed and more preferably, group other than hydrogen. [0048] Unless otherwise specified, all isomers are included in the invention. For example, alkyl, alkylene and alkenylene includes straight-chain or branched-chain ones. Double bond in alkenylene include structure of configurations E, Z and EZ mixtures. Isomers generated by asymmetric carbon(s) e.g. branched alkyl are also included in the present invention. [0049] In the compounds of the formula (I) of the present invention, the compounds wherein and is C5-15 carbocyclic ring and Z⁵ is C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, or group containing phenyl or C3-7 cycloalkyl (each ring may be substituted.) are preferable. The compounds wherein and is mono- or bi-ring of C5-10 carbocyclic aryl and C5-7 cycloalkyl and Z⁵ is the above mentioned group are more pref-[0050] The compounds wherein at least one of and Z⁵ is 5-7 membered heterocyclic ring containing one or two oxygen, sulfur or nitrogen atom(s) (each ring may be substituted.) are also preferable. Such compounds include, for example, the compounds wherein (1)

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and

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	is C5-15 carbocyclic ring and Z^5 is 5-7 membered heterocyclic ring containing one or two oxygen, sulfur or nitrogen atom(s) or (2) one of
10	A
15	and
20	В
	is 5-7 membered heterocyclic ring containing one or two oxygen, sulfur or nitrogen atom(s) and the other is C5-15 car- bocyclic ring. The compounds wherein carbocyclic ring represented by
25	A
30	and/or
35	B
	in case of the above (1) and (2) is mono- or bi-ring of C5-10 carbocyclic aryl and C5-7 cycloalkyl are more preferable. [0051] In the compounds of the formula (I) of the present invention, concrete and preferable compounds include the compounds described in the Examples and corresponding esters and amides.
40	[Salt]
45	[0052] The compounds of the present invention of the formula (I) maybe converted into the corresponding salts by methods known per se. Non-toxic and water-soluble salts are preferable. Suitable salts, for example, are as follows:

50 [The method of the preparation for the present invention compounds]

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tris(hydroxymethyl)aminomethane, lysine, arginine, N-methyl-D-glucamine etc.).

[0053] The compounds of the formula (I) of the present invention may be prepared by the method described in the following, the method described in the Examples as hereinafter or known methods.

45 salts of alkali metals (potassium, sodium etc.), salts of alkaline earth metals (calcium, magnesium etc.), ammonium salts, salts of pharmaceutically acceptable organic amines (tetramethylammonium, triethylamine, methylamine, direthylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine,

(1) In the compounds of the formula (I) of the present invention, the carboxylic acid compounds of the formula (Ia)

$$(R^{3})n - B = Z^{1a} - Z^{1a}$$

$$(Z^{2a})t = Z^{3} - N - Z^{4} - Z^{5}$$

$$R^{4}$$
(Ia)

(wherein Z^{1a} and Z^{2a} are as Z^1 and Z^2 , respectively, with the proviso that at least one of them is COOH or a group containing COOH, and the other symbols are as hereinbefore defined.) may be prepared from the ester compound of the formula (lb)

$$(R^{3b})n - B = Z^{3-N} - Z^{4-} Z^{5b}$$
(Ib)

(wherein Z^{1b} and Z^{2b} are as Z^1 and Z^2 , respectively, with the proviso that at least one of them is COR^{1b} or a group containing COR^{1b} (wherein R^{1b} is C1-4 alkoxy or methoxymethoxy (abbreviated as OMOM.).), R^{3b}, R^{4b} and Z^{5b} are as R³, R⁴ and Z^{5} , respectively, with the proviso when R³, R⁴ or R⁵ in Z⁵ is COOH or hydroxy, or a group containing COOH or hydroxy, each COOH and hydroxy is protected by a protecting group which is removable under an acidic, neutral or alkaline condition, and the other symbols are as hereinbefore defined.) by hydrolysis under an alkaline, acidic or neutral condition, if necessary, followed by hydrolysis under the different condition.

The removal of a protecting group by hydrolysis under an alkaline, acidic or neutral condition is a well-known reaction as hereinafter described.

(2) In the compounds of the formula (I) of the present invention, the ester compounds of the formula (Ic)

$$(R^{3})n - B = Z^{3} - N - Z^{4} - Z^{5}$$

$$(Ic)$$

(wherein Z^{1c} and Z^{2c} are as Z^1 and Z^2 , respectively, with the proviso that at least one of them is COR^{1c} or a group containing COR^{1c} (wherein R^{1c} is C1-4 alkoxy.) and the other symbols are as hereinbefore defined.) may be prepared from the compound of the formula (la) by esterification.

Esterification is well known, it may be carried out, for example:

- (a) by the method using diazoalkane,
- (b) by the method using alkyl halide,
- (c) by the method using dimethylformamide (DMF)-dialkyl acetal or

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(d) by the method reacting corresponding alkanol etc.

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Concrete description of the methods described above are as follows:

- (a) The method using diazoalkane may be carried out, for example, using corresponding diazoalkane in an organic solvent (diethylether, ethyl acetate, methylene chloride, acetone, methanol or ethanol etc.) at -10~40°C.
- (b) The method using alkyl halide may be carried out, for example, in an organic solvent (acetone, DMF, dimethylsufoxide (DMSO) etc.) in the presence of base (potassium carbonate, sodium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, calcium oxide etc.) using corresponding alkyl halide at -10~40°C.
- (c) The method using DMF-dialkyl acetal may be carried out, for example, in an organic solvent (benzene, toluene etc.) using corresponding DMF-dialkyl acetal at -10~40°C.
- (d) The method of reacting corresponding alkanol may be carried out, for example, in corresponding alkanol (HR 1c (R 1c is as hereinbefore defined.)) using acid (HCl, sulfuric acid, p-toluene sulfonic acid, hydrochloride gas etc.) or condensing agents (DCC, pivaloyl halide, aryl sulfonyl halide, alkyl sulfonyl halide etc.) at 0~40°C.

Of course, an organic solvent (tetrahydrofuran, methylene chloride etc.) which does not relate to the reaction may be added in these esterification.

(3) In the compounds of the formula (I) of the present invention, the amide compounds of the formula (Id)

$$(R^{3})n - B = Z^{3-N-}Z^{4-}Z^{5}$$
(Id)

(wherein Z^{1d} and Z^{2d} are as Z¹ and Z², respectively, with the proviso that at least one of them is COR^{1d} or a group containing COR^{1d} (wherein R^{1d} is NR⁶R⁷ (wherein all symbols are as hereinbefore defined.), and the other symbols are as hereinbefore defined.) may be prepared by reacting the compound of the formula (III)

(wherein all symbols are as hereinbefore defined.) to form the amide bond.

Reaction to form amide-bond is well known, it may be carried out, for example, in an organic solvent (THF, methylene chloride, benzene, acetone, acetonitrile etc.), in the presence or absence of tertiary amine (dimethylaminopyridine, pyridine, triethylamine etc.) using a condensing agent (EDC or DCC etc.) at 0~50°C.

(4) In the compounds of the formula (I) of the present invention, the alcohol compounds of the formula (Ie)

$$(R^{3})n - B = Z^{1-e}$$

$$(Z^{2})t$$

$$Z^{3}-N-Z^{4}-Z^{5}$$

$$R^{4}$$
(Ie)

(wherein Z^{1e} is C1-5 alkylene-OH, and the other symbols are as hereinbefore defined.) may be prepared by the reduction of the compound of the formula (if)

$$(R^{3})n - B = Z^{3} - N - Z^{4} - Z^{5}$$

$$(If)$$

(wherein Z^{1f} is COOY^f or C1-4 alkylene-COOY^f (wherein Y^f is C1-4 alkyl.), and the other symbols are as hereinbefore defined.).

The reductive reaction is known, and for example, this reaction may be carried out in the presence of organic solvent (THF, methylene chloride, diethylether, lower alkanol etc.) using lithium aluminum hydride (LAH) or diisobutyl aluminum hydride (DIBAL) at -78°C to room temperature.

(5) In the compounds of the formula (lb), wherein R² is CONR⁸, C1-4 alkylene-CONR⁸, CONR⁸-C1-4 alkylene, C1-3 alkylene-CONR⁸-C1-3 alkylene, (wherein all symbols are as hereinbefore defined.), i.e. the compounds of the formula (lb-1)

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$$(R^{3b}) n - B = Z^{1b}$$

$$(Z^{2b}) t$$

(wherein R²⁰ is CONR⁸, C1-4 alkylene-CONR⁸, CONR⁸-C1-4 alkylene, C1-3 alkylene-CONR⁸-C1-3 alkylene, (wherein all symbols are as hereinbefore defined.), and the other symbols are as hereinbefore defined.) may be prepared by reacting the compound of the formula (IV)

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$$(R^{3b})n - B = Z^{3-N-Z^4-Z^{5b}}$$

$$R^{4b}$$
(IV)

(wherein R^{200} is single bond or C1-4 alkylene, and the other symbols are as hereinbefore defined.) with the compound of the formula (V)

$$R^{8}HN-R^{201}$$
 A Z^{1b} (V)

(wherein R²⁰¹ is single bond or C1-4 alkylene, and the other symbols are as hereinbefore defined.) to form amide bond.

Reaction to form amide bond may be carried out as the method described in the said (3).

(6) In the compounds of the formula (lb), wherein R² is NR⁸CO, C1-4 alkylene-NR⁸CO, NR⁸CO-C1-4 alkylene, C1-3 alkylene-NR⁸CO-C1-3 alkylene (wherein all symbols are as hereinbefore defined.), i.e. the compounds of the formula (lb-2)

$$(R^{3b})n - B = Z^{3-1} - Z^{4-1} - Z^{5b}$$

$$Z^{3-1} - Z^{4-1} - Z^{5b}$$

$$R^{4b}$$
(Ib-2)

(wherein R²¹ is NR⁸CO, C1-4 alkylene-NR⁸CO, NR⁸CO-C1-4 alkylene, C1-3 alkylene-NR⁸CO-C1-3 alkylene (wherein all symbols are as hereinbefore defined.), and the other symbols are as hereinbefore defined.) may be prepared by reacting the compound of the formula (VI)

$$(R^{3b})n - B = Z^{3} - N - Z^{4} - Z^{5b}$$

$$R^{4b}$$
(VI)

(wherein all symbols are as hereinbefore defined.) with the compound of the formula (VII)

HOOC-R²⁰¹
$$(VII)$$

(wherein all symbols are as hereinbefore defined.) to form amide bond.

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Reaction to form amide bond may be carried out as the method described in the said (3).

(7) In the compounds of the formula (lb), wherein R² is O, S, NZ⁶, Z⁷-C1-4 alkylene, C1-4 alkylene-NZ⁷ or C1-3 alkylene-NZ⁷-C1-3 alkylene (wherein all symbols are as hereinbefore defined.), i.e. the compounds of the formula (lb-3)

$$(R^{3b})n - B = Z^{1b} - Z^{1b}$$

$$(Z^{2b})t = Z^{3-N-Z^4-Z^{5b}}$$

$$R^{4b} = Z^{1b} - Z^{1b}$$

$$(Ib-3)$$

(wherein R²² is O, S, NZ⁶, Z⁷-C1-4 alkylene, C1-4 alkylene-NZ⁷ or C1-3 alkylene-NZ⁷-C1-3 alkylene (wherein all symbols are as hereinbefore defined.).)
may be prepared by reacting the compound of the formula (VIII)

$$(R^{3b})n - B$$
 $(Z^{2b})t$
 $(Z^{2b})t$
 $(VIII)$

(wherein all symbols are as hereinbefore defined.) with the compound of the formula (IX)

$$X-Z^4-Z^{5b} \tag{IX}$$

(wherein X is halogen and the other symbols are as hereinbefore defined.) to form sulfonamide bond or carboamide bond.

Reactions to form sulfonamide bond or carbcamide bond may be carried out, for example, in an organic solvent (THF, methylene chloride, benzene, acetone, acetonitrile etc.), in the presence or absence of tertiary amine (dimethylaminopyridine, pyridine, triethylamine etc.) at 0~50°C.

(8) In the compounds of the formula (lb), wherein R^2 is NZ^6 -C1-4 alkylene, C1-4 alkylene- NZ^6 or C1-3 alkylene (wherein all symbols are as hereinbefore defined.), i.e. the compounds of the formula (lb-4)

$$(R^{3b})n - B = Z^{3} - 1 - Z^{1b}$$

$$(Z^{2b})t = Z^{3} - N - Z^{4} - Z^{5b}$$

$$(B^{3b})n - B = Z^{3} - N - Z^{4} - Z^{5b}$$

(wherein R²³ is NZ⁶-C1-4 alkylene, C1-4 alkylene-NZ⁶ or C1-3 alkylene-NZ⁶-C1-3 alkylene (wherein all symbols are as hereinbefore defined.) and the other symbols are as hereinbefore defined.) may be prepared by

(a) reacting (reductive amination) the compound of the formula (VI-a)

$$(R^{3b})n - B$$

$$= Z^{3} - N - Z^{4} - Z^{5b}$$

$$= R^{230} - N + Z^{6}$$

$$= Z^{3} - N - Z^{4} - Z^{5b}$$

(wherein R^{230} is single bond or C1-4 alkylene, and the other symbols are as hereinbefore defined.) with the compound of the formula (VII-a)

HOC-R²³¹
$$A$$
 Z^{1b} (VII-a)

(wherein R²³¹ is single bond or C1-3 alkylene, and the other symbols are as hereinbefore defined.) or (b) reacting (reductive amination) the compound of the formula (VI-b)

$$(R^{3b})n - B$$

$$Z^{3}-N-Z^{4}-Z^{5b}$$

$$R^{4b}$$
(VI-b)

(wherein all symbols are as hereinbefore defined.) with the compound of the formula (VII-b)

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$$HZ^{6}N-R^{230}$$
 (VII-b)

(wherein all symbols are as hereinbefore defined.).

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The reaction of reductive amination described in the above (a) and (b) may carried out, for example, in organic solvent (methanol etc.), in an acidic condition, using a boron reagent such as sodium cyanoborohydride etc. at 0~50°C.

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(9) In the compounds of the formula (lb), wherein R² is C2-4 alkenylene, i.e. the compounds of the formula (lb-5)

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$$(R^{3b})n - B = Z^{3-1} A Z^{1b}$$

$$(Z^{2b})t \qquad (Ib-5)$$

$$Z^{3-1} - Z^{4-1} Z^{5b}$$

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(wherein R^{25} is C2-4 alkenylene and the other symbols are as hereinbefore defined.) may be prepared by reacting the compound of the formula (XI)

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$$(R^{3b})n$$
 R^{25}
 $(Z^{2b})t$
 (XI)

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(wherein all symbols are as hereinbefore defined.) with the compound of the formula (IX)

 $X-Z^4-Z^{50} \tag{IX}$

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(wherein all symbols are as hereinbefore defined.)
to form sulfonamide bond or carboamide bond

to form sulfonamide bond or carboamide bond.

Reaction to form sulfonamide bond or carboamide bond may be carried out as the method described in the

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said (7).

(10) In the compounds of the formula (lb), wherein R² is C2-4 alkylene, i.e. the compounds of the formula (lb-6)

$$(R^{3b})n - B = Z^{16} - 1 - A - (Z^{2b})t$$

$$(R^{3b})n - B = Z^{3-}N - Z^4 - Z^{5cc}$$

$$R^{4cc}$$
(Ib-6)

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(wherein R²⁶ is C2-4 alkylene, Z^{1cc}, Z^{5cc} and Z^{4cc} are as Z^{1b}, Z^{5b} and Z^{4b}, respectively, with the proviso that none of Z^{1cc}, Z^{5cc} and Z^{4cc} are alkylenylene, alkynylene-containing group and alkynylene-containing group, and the other symbols are as hereinbefore defined.) may be prepared by catalytic reduction of the compound of the formula (lb-5).

The catalytic reduction is known, and for example, this reaction may be carried out under the condition of atmosphere of hydrogen gas, in an organic solvent (THF, alkanol or acetone etc.), using a reductive catalyst (Pd, Pd-C, Pt or platinum oxide etc.) at 0~50°C.

(11) In the compounds of the formula (lb), wherein R2 is C2-4 alkynylene, i.e. the compounds of the formula (lb-7)

$$(R^{3b})n - B$$

$$= Z^{3-1} - Z^{1b}$$

$$= Z^{3-1} - Z^{4-1} - Z^{5b}$$

$$= Z^{3-1} - Z^{4-1} - Z^{5b}$$

$$= Z^{4-1} - Z^{5b}$$

$$= Z^{4-1} - Z^{5b}$$

(wherein R²⁷ is C2-4 alkynylene, and the other symbols are as hereinbefore defined.) may be prepared by reacting the compound of the formula (XII)

$$(R^{3b})n$$
 B
 Z^{1b}
 $(Z^{2b})t$
 Z^{3}
 Z^{3}

(wherein all symbols are as hereinbefore defined.) with the compound of the formula (IX)

$$X-Z^4-Z^{50}$$
 (IX)

(wherein all symbols are as hereinbefore defined.) to form sulfonamide bond or carboamide bond.

Reaction to form sulfonamide bond or carboamide bond may be carried out as the method described in the said (7).

(12) In the compounds of the formula (lb), wherein R² is NZ⁶SO₂ (wherein all symbols are as hereinbefore defined.), i.e. the compounds of the formula (lb-8)

$$(R^{3b})n - B = Z^{1b} - (Z^{2b})t$$

$$Z^{3-}N - Z^{4-}Z^{5b}$$

$$R^{4b}$$
(Ib-8)

(wherein R^{28} is NZ^6SO_2 (wherein a' symbols are as hereinbefore defined.), and the other symbols are as hereinbefore defined.)

may be prepared by reacting the compound of the formula (Z-1)

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$$(R^{3b})n - B = Z^3 - N - Z^4 - Z^{5b}$$

$$R^{4b}$$
(Z-1)

(wherein all symbols are as hereinbefore defined.) with the compound of the formula (Z-2)

$$XO_2S \xrightarrow{1} A Z^{1b}$$
 (Z-2)

(wherein all symbols are as hereinbefore defined.) to form sulfonamide bond.

Reaction to form sulfonamide bond may be carried out as the method described in the said (7).

40 (13) In the compounds of the formula (lb), wherein R² is CO, CO-C1-4 alkylene, C1-4 alkylene-CO or C1-3 alkylene-CO-C1-3 alkylene, i.e. the compounds of the formula (lb-9)

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$$(R^{3b})n - B = Z^{3-} N - Z^{4-} Z^{5b}$$

$$(R^{3b})n - B = Z^{3-} N - Z^{4-} Z^{5b}$$

$$R^{4b}$$
(Ib-9)

(wherein R²⁹ is CO, CO-C1-4 alkylene, C1-4 alkylene-CO or C1-3 alkylene-CO-C1-3 alkylene, and the other symbols are as hereinbefore defined.) may be prepared by reacting the compound of the formula (Z-3)

$$(R^{3b})n$$
 B
 $Z^{3-}N$
 $Z^{4-}Z^{5b}$
 C^{5b}
 C^{5b}
 C^{5b}

(wherein all symbols are as hereinbefore defined.) with the compound of the formula (Z-4)

$$X-R^{201}$$
 A Z^{1b} $(Z-4)t$

(wherein all symbols are as hereinbefore defined.)

This reaction may be carried out, for example, in organic solvent (THF, methylene chloride, benzene, acetone, acetonitrile etc.) in the presence of Zn or cyano copper at -78°C to room temperature.

(14) In the compounds of the formula (lb), wherein R^{4b} is group other than H, i.e. the compounds of the formula (lb-10)

$$(R^{3b})n$$
 B
 Z^{1b}
 $(Z^{2b})t$
 Z^{1b}
 Z^{1b}
 Z^{2b}
 Z^{2b}

(wherein R⁴⁴ is as R⁴ other than H, and the other symbols are as hereinbefore defined.) may be prepared by reacting the compound of the formula (lb-11)

$$(R^{3b})n - B$$

$$= Z^{3-N} - Z^{4-} Z^{5b}$$

$$= Z^{3-N} - Z^{4-} Z^{5b}$$

$$= Z^{4-} Z^{5b}$$

(wherein all symbols are as hereinbefore defined.) and (a) the compound of the formula (Z-5)

$$X = R^{44}$$
 (Z-5)

(wherein all symbols are as hereinbefore defined.) or (b) the compound of the formula (Z-6)

$$HO_{--}R^{44}$$
 (Z-6)

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(wherein all symbols are as hereinbefore defined.).

The above reaction is N-alkylation reaction or corresponding reaction. For example, this reaction (a) in case of using alkyl halide of the formula

X-R44

(wherein all symbols are as hereinbefore defined.),

may be carried out in organic solvent (acetone, THF or methylene chloride etc.), in the presence of base (potassium carbonate etc.) at 0~50°C.

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The reaction (b) in case of using alcohol of the formula

HO-R44

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(wherein all symbols are as hereinbefore defined.),

may be carried out in organic solvent (acetone, THF or methylene chloride etc.), in the presence of triphenylphosphine and diethyldiazocarboxylate (DEAD) at 0~50°C.

- (15) The compounds wherein R³ is hydroxymethyl may be prepared by the method mentioned above or the method described in the Examples hereinafter.
- (16) The compounds wherein Z^4 is SO_2 and Z^5 is cyclopentyl, cyclohexyl (each ring may be substituted by 1-5 of R^5 (R^5 is as hereinbefore defined.).) or isopropyl may be prepared by the method mentioned above or the method described in the Examples hereinafter.

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(17) The compounds wherein symbol(s) other than Z¹ is/are COOH, COOZ^a (wherein Z^a is C1-4 alkyl) or hydroxy or group containing COOH, COOZ^a (wherein Z^a is as hereinbefore defined.) or hydroxy may be prepared by reacting under the condition that each of the above groups and Z¹ if necessay are protected

may be prepared by reacting under the condition that each of the above groups and Z¹ if necessay are protected by a protecting group which is removable under an alkaline, acidic or neutral condition and removing a protecting group under an alkaline, acidic or neutral condition or combining removal of protecting groups under different conditions (for example, removal of a protecting group under an acidic condition and removal of a protecting group under an alkaline condition may be carried out successively, either reaction being started first.).

[0054] A protecting group of COOH which is removable under an acidic condition includes, for example, silyl containing group such as t-butyldimethylsilyl etc. or t-butyl.

[0055] A protecting group of COOH which is removable under an alkaline condition includes alkyl group (for example, methyl etc.) other than t-butyl.

[0056] A protecting group of COOH which is removable under both an acidic condition and an alkaline condition includes, for example, methoxymethyl.

[0057] A protecting group of COOH which is removable under a neutral condition includes benzyl etc.

[0058] A protecting group of hydroxy which is removable under an acidic condition includes, for example, tetrahydoropyranyl, silyl containing group such as t-butyldimethylsilyl etc. 1-ethoxyethyl or methoxymethyl etc.

[0059] A protecting group of hydroxy which is removable under an alkaline condition includes acyl group such as acetyl etc.

[0060] A protecting group of hydroxy which is removable under a neutral condition includes benzyl or silyl containing group such as t-butyldimethylsilyl etc.

[0061] The removal of a protecting group under an alkaline condition is well known. For example, this reaction may be carried out in an organic solvent (methanol, THF, dioxane etc.), using a hydroxide of an alkali metal (sodium hydroxide, potassium hydroxide etc.), a hydroxide of an alkaline earth metal (calcium hydroxide etc.) or a carbonate salt (sodium carbonate, potassium carbonate etc.) or an aqueous solution thereof, or mixture thereof at 0~40°C.

[0062] The removal of a protecting group under an acidic condition is well known. For example, this reaction may be carried out in a solvent (methylene chloride, dioxane, ethyl acetate, acetic acid, water or mixture thereof etc.), using an organic acid (trifluoroacetic acid etc.) or an inorganic acid (HCl, HBr etc.) at 0~120°C.

The removal of a protecting group under a neutral condition is well known. For example, this reaction using benzyl may be carried out in a solvent (ether (THF, dioxane, dimethoxyethane, diethyl ether etc.), alcohol (methanol, ethanol etc.), benzene (benzene, toluene etc.), ketone (acetone, methylethyl ketone etc.), nitrile (acetonitrile etc.) amide (dimethylformamide etc.) water, ethyl acetate, acetic acid or mixture thereof etc.) in the presence of catalyst (Pd-C, palladium black, PdOH, PtO2, Raney nickel etc.), at ordinary or increased pressure under the condition of atmosphere of hydrogen gas or in the presence of ammonium formate at 0~200°C.

[0064] This reaction using silyl containing group such as t-butyldimethylsilyl etc. may be carried out in a solvent such as ether (THF etc.), using tetrabutylammonium fluoride at 0~50°C.

[0065] The compounds of the formula (III), (V), (VII), (IX), (VII-a), (VII-b), (Z-2), (Z-4), (Z-5) or (Z-6) are known or may be prepared easily by known methods or the methods described in the Examples hereinafter. The compounds of the formula (IV), (VI), (VIII), (X), (XI), (XII) or (Z-3) may be prepared by the following reaction schemes (A)-(F).

[0066] In each reaction scheme, each symbol is as hereinbefore defined, or as defined as follows.

R²⁰⁰ : single bond or C1-4 alkylene; R²⁰² : single bond or C1-4 alkylene; 15 R²⁰³ : single bond or C1-4 alkylene; R²⁰⁴: single bond or C1 or 2 alkylene; R²⁰⁵: C1, 2 or 3 alkylene; R²⁰⁶: single bond or C1 or 2 alkylene; R²⁰⁷: C1, 2 or 3 alkylene; 20 R²⁰⁸ : C1 or 2 alkylene; R⁵⁰ : C1-4 alkyl; R⁵¹: trifluoroacetyl: X1, X2, X3, X4: halogen. 25

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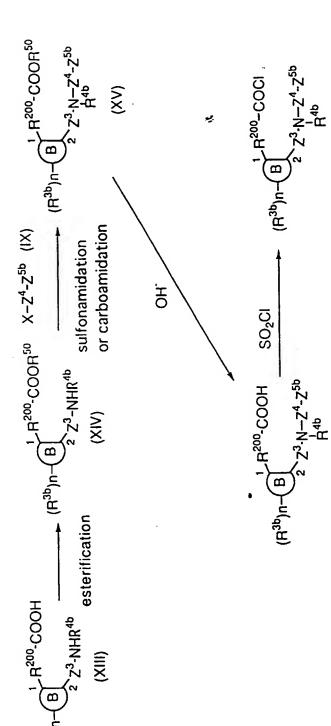
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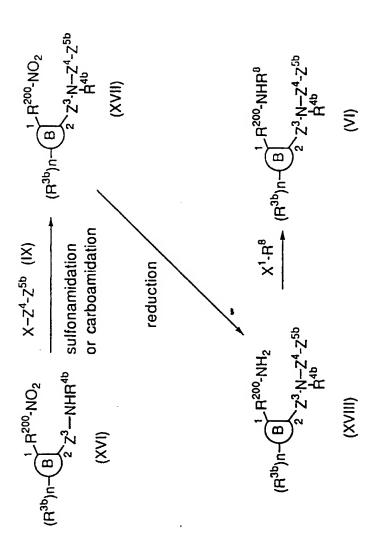
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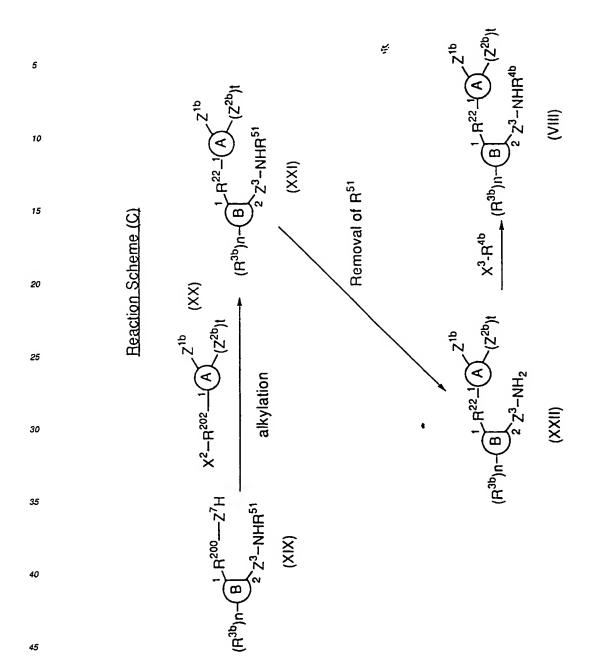
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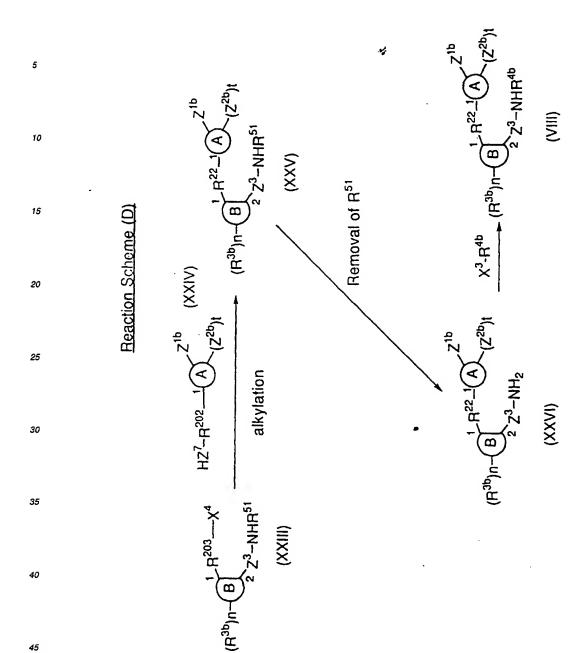
Reaction Scheme (A)



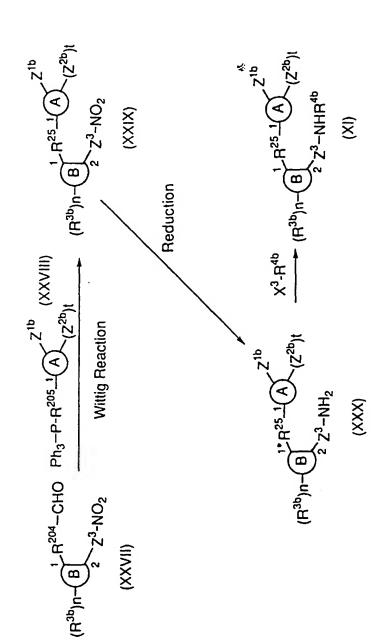
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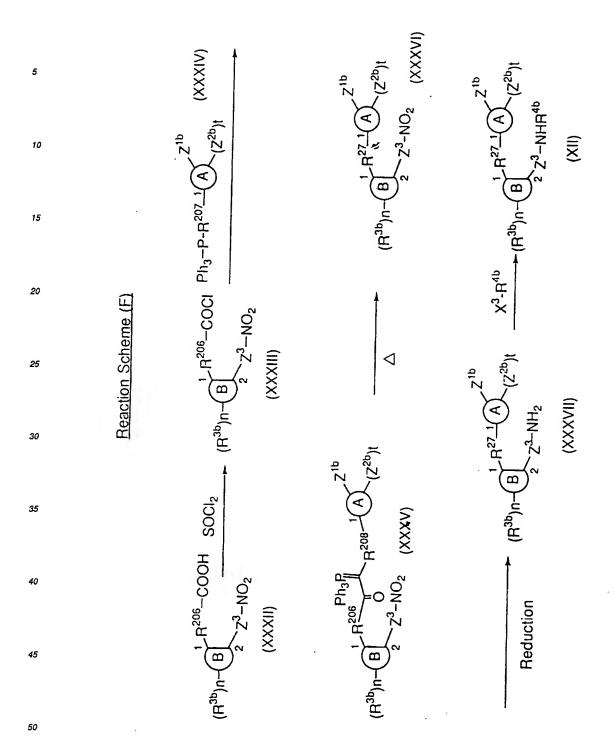






Reaction Scheme (E)





[0067] In each reaction in the present specification, obtained products may be purified by conventional techniques.

For example, purification may be carried out by distillation at atmospheric or reduced pressure, by high performance liquid chromatography, by thin layer chromatography or by column chromatography using silica gel or magnesium silicate, by washing or by recrystallization. Purification may be carried out after each reaction, or after a series of reactions.

[Starting materials and reagents]

[0068] The other starting materials and reagents in the present invention are known per se or may be prepared by known methods.

Industrial Availability

[Pharmacological activity of the present invention compounds]

[0069] The compounds of the present invention of the formula (I) can bind to the receptors of prostaglandin E₂ and show antagonistic activity against the action thereof or agonistic activity, so they are useful as PGE₂ antagonists or agonists.

[0070] As mentioned hereinbefore, to antagonize against PGE₂ is linked to inhibition of uterine contraction, analgesic action, inhibition of digestive peristalsis, induction of sleep or increase of vesical capacity. Therefore, PGE₂ antagonists are considered to be useful for the prevention of abortion, as analgesics, as antidiarrheals, as sleep inducers or as agents for treating pollakiuria.

[0071] As mentioned hereinbefore, to show PGE₂ agonistic activity is linked to uterine contraction, promotion of digestive peristalsis, suppression of gastric acid secretion or reduction of blood pressure or diuresis. Therefore, PGE₂ agonists are considered to be useful as abortifacient, cathartic, antiulcer, anti-gastritis, antihypertensive or diuretic agents. [0072] For example, in standard laboratory test, it was confirmed that the compounds of the formula (I) of the present invention can bind to receptor of PGE₂ (EP₁ receptor) according to assay using expression cell of prostanoid receptor subtype.

(i) Binding assay using expression cell of prostanoid receptor subtype

[0073] The preparation of membrane fraction was carried out according to the method of Sugimoto et al (J. Biol. Chem. 267, 6463-6466 (1992)), using expression CHO cell of prostanoid receptor subtype (mouse EP1).

[0074] The standard assay mixture contained membrane fraction (0.5 mg/ml), ³H-PGE₂ in a final volume of 200 ml was incubated for 1 hour at room temperature. The reaction was terminated by addition of 3 ml of ice-cold buffer. The mixture was rapidly filtered through a glass filter (GF/B). The radioactivity associated with the filter was measured by liquid scintillation counting.

[0075] Kd and Bmax values were determined from Scatchard plots (Ann. N.Y. Acad. Sci, <u>51</u>, 660 (1949)). Non-specific binding was calculated as the bond in the presence of an excess (2.5 nM) of unlabeled PGE₂. In the experiment for competition of specific ³H-PGE₂ binding by the compounds of the present invention, ³H-PGE₂ was added at a concentration of 2.5 nM and the compound of the present invention was added at a concentration of 1 µM. The following buffer was used in all reaction.

Buffer: potassium phosphate (pH6.0, 10 mM), EDTA (1 mM), MgCl₂ (10 mM), NaCl (0.1 M).

The dissociation constant Ki (μM) of each compound was calculated by the following equation.

$$Ki = IC50/(1+([C]/Kd))$$

The results were shown in Table 1.

Table 1

Example No.	dissociation constant Ki (μΜ)
2 (k)	0.099
18 (30)	0.0016
18 (38)	0.016
18 (58)	0.0062
18 (75)	0.0054
18 (94)	0.0004
18 (102)	0.0002

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Table 1 (continued)

Example No.	dissociation constant Ki (μM)
20 (20)	0.0099
22 (3)	0.48
24	0.0058
24 (9)	0.018
30	0.073
38	0.16
43	0.38
44	0.0013
48	0.01

[Toxicity]

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[0076] The toxicity of the compounds of the present invention is very low and therefore, it is confirmed that these compounds are safe for use as medicine.

[Application for Pharmaceuticals]

[0077] The compounds of the present invention of the formula (I) can bind to the receptors of prostaglandin E_2 and show antagonistic activity against the action thereof or agonistic activity, so they are useful as PGE_2 antagonists or agonists.

[0078] As mentioned hereinbefore, to antagonize against PGE₂ is linked to inhibition of uterine contraction, analgesic action, inhibition of digestive peristalsis, induction of sleep or increase of vesical capacity. Therefore, PGE₂ antagonists are considered to be useful for the prevention of abortion, as analgesics, as antidiarrheals, as sleep inducers or as agents for treating pollakiuria.

[0079] As mentioned hereinbefore, to show PGE_2 agonistic activity is linked to uterine contraction, promotion of digestive peristalsis, suppression of gastric acid secretion or reduction of blood pressure or diuresis. Therefore, PGE_2 agonists are considered to be useful as abortifacient, cathartic, antiulcer, anti-gastritis, antihypertensive or diuretic agents. [0080] The compounds of the present invention can bind to receptors of prostaglandin E_2 , especially, EP1 receptor strongly, so they are expected to be useful as analgesics or as agents for treating pollakiuria.

[0081] For the purpose above described, the compounds of the formula (I), non-toxic salts thereof and hydrates thereof may be normally administered systemically or locally, usually by oral or parenteral administration.

[0082] The doses to be administered are determined depending upon age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment etc. In the human adult, the doses per person per dose are generally between 1 µg and 100 mg, by oral administration, up to several times per day, and between 0.1 µg and 10 mg, by parenteral administration (preferred into vein) up to several times per day, or continuous administration between 1 and 24 hours per day into vein.

5 [0083] As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

[0084] On administration of the compounds of the present invention, it is used as solid compositions, liquid compositions or other compositions for oral administration, as injections, liniments or suppositories etc. for parenteral administration.

[0085] Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules etc.

[0086] Capsules contain hard capsules and soft capsules.

[0087] In such solid compositions, one or more of the active compound(s) is or are, admixed with at least one inert diluent such as lactose, mannitol, mannit, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminat. The compositions may also comprise, as is normal practice, additional substances other than inert diluents: e.g. lubricating agents such as magnesium stearate, disintegrating agents such as cellulose calcium glycolate, and assisting agents for dissolving such as glutamic acid or asparaginic acid. The tablets or pills may, if desired, be coated with film of gastric or enteric material such as sugar, gelatin, hydroxypropyl cel-

lulose or hydroxypropyl cellulose phthalate etc., or be coated with two or more films. And further, coating may include containment within capsules of absorbable materials such as gelatin.

[0088] Liquid compositions for oral administration include pharmaceutically-acceptable emulsions, solutions, syrups and elixirs etc. In such liquid compositions, one or more of the active compound(s) is or are comprised in inert diluent(s) commonly used in the art (for example, purified water, ethanol etc.). Besides inert diluents, such compositions may also comprise adjuvants such as wetting agents, suspending agents, sweetening agents, flavouring agents, perfuming agents and preserving agents.

[0089] Other compositions for oral administration include spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s). Spray compositions may comprise additional substances other than inert diluents: e.g. stabilizing agents such as sodium hydrogen sulfate, stabilizing agents to give the title compound isotonicity, isotonic buffer such as sodium chloride, sodium citrate, citric acid. For preparation of such spray compositions, for example, the method described in the United States Patent No. 2868691 or 3095355 may be used.

[0090] Injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. Aqueous solutions or suspensions include distilled water for injection and physiological salt solution. Non-aqueous solutions or suspensions include propylene glycol, polyethylene glycol, plant oil such as clive oil, alcohol such as ethanol, POLYSORBATE80 (registered trade mark) etc. Such compositions may comprise additional diluents: e.g. preserving agents, wetting agents, emulsifying agents, dispersing agents, stabilizing agent, assisting agents such as assisting agents for dissolving (for example, glutamic acid, asparaginic acid). They may be sterilized for example, by filtration through a bacteria-retaining filter, by incorporation of sterilizing agents in the compositions or by irradiation. They also be manufactured in the form of sterile solid compositions and which can be dissolved in sterile water or some other sterile diluents for injection immediately before used.

[0091] Other compositions for parenteral administration include liquids for external use, and endemic liniments, ointment, suppositories and pessaries which comprise one or more of the active compound(s) and may be prepared by known methods.

Best mode to practice the invention

[0092] The following reference examples and examples are intended to illustrate, but not limit, the present invention.
[0093] The solvents in parentheses show the developing or eluting solvents and the ratios of the solvents used are by volume in chromatographic separations. Without special explanation, NMR data was determined in CDCl₃ solution.

Reference Example 1

5-chloro-anthranilic acid methyl ester

[0094]

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[0095] To a suspension of 5-chloroanthranilic acid (6.1 g) in AcOEt-MeOH (20 ml + 10 ml), a solution of an excess amount of diazomethane in ether (50 ml) was added at 0°C. After termination of reaction, reaction solvent was evaporated to dryness to give the title compound (6.6 g) having the following physical data.

NMR: δ 7.82 (1H, d), 7.21 (1H, dd), 6.60 (1H, d), 5.73 (2H, brs), 3.88 (3H, s).

Reference Example 2

Methyl 2-phenylsulfonylamino-5-chlorobenzoate

5 [0096]

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CI COOMe
O2
N
H

[0097] T

[0097] To a solution of 5-chloro-anthranilic acid methyl ester (400 mg; prepared in Reference Example 1.) and pyridine (0.87 ml) in methylene chloride, benzenesulfonylchloride (0.33 ml) was added at 0°C. The solution was stirred overnight at room temperature. The reaction mixture was poured into diluted HCl and extracted with ethyl acetate. The organic layer was washed, dried over and concentrated under reduced pressure. The residue was purified on silica gel column chromatography (hexane-AcOEt) to give the title compound (664 mg) having the following physical data.

TLC: Rf 0.30 (hexane: AcOEt = 4:1); NMR: δ 10.5 (1H, s), 7.90-7.79 (3H, m), 7.79 (1H, d), 7.60-7.37 (4H, m), 3.88 (3H, s).

Reference Example 3

2-phenylsulfonylamino-5-chlorobenzoic acid

[0098]

CI COOH
O2
N S

40

[0099] To a solution of methyl 2-phenylsulfonylamino-5-chlorobenzoate (600 mg; prepared in Reference Example 2.) in the mixture of THF-MeOH (6 ml + 3 ml), 2N NaOH solution (2 ml) was added. The mixture was stirred for 2 days. To the reaction mixture, 1N HCl (4.5 ml) was added. The mixture was extracted with ethyl acetate. The organic layer was washed and dried over to give the title compound (575 mg) having the following physical data.

NMR: δ 10.31 (1H, s), 7.99 (1H, d), 7.92-7.83 (2H, m), 7.70 (1H, d), 7.63-7.42 (4H, m), 6.20 (1H, brs).

50

Example 1

Methyl 4-(2-phenylsulfonylamino-5-chlorobenzoylamino)benzoate

5 [0100]

20

COOME

NH

SO2

[0101] To a suspension of 2-phenylsulfonylamino-5-chlorobenzoic acid (250 mg; prepared in Reference Example 3.) and methyl p-aminobenzoate (133 mg) in methylene chloride (5 ml), EDC (168 mg) and dimethylaminopyridine (20 mg) were added. The mixture was stirred for 3 days at room temperature. The reaction mixture was poured into diluted HCl and extracted with ethyl acetate. The organic layer was washed, dried over and concentrated under reduced pressure. The residue was purified on silica gel column chromatography (AcOEt-benzene) to give the title compound (142 mg)

 30 TLC : Rf 0.29 (AcOEt : benzene = 1 : 9); NMR (CDCl₃+DMSO-d₆) : δ 10.40 (1H, s), 9.90 (1H, m), 8.03 (2H, d), 7.82-7.70 (5H, m), 7.63 (1H, d), 7.50-7.24 (4H, m), 3.93 (3H, s).

Example 2

having the following physical data.

4-(2-phenylsulfonylamino-5-chlorobenzoylamino)benzoic acid

[0102]

35

45 COOH

NH

SO2

50

55 [0103] To a solution of methyl 4-(2-phenylsulfonylamino-5-chlorobenzoylamino)benzoate (122 mg; prepared in Example 1.) in THF-MeOH (4 ml + 2 ml), 2N NaOH aqueous solution (0.5 ml) was added at room temperature. The mixture was stirred overnight. To the reaction mixture, 2N HCl (0.6 ml) and water were added. The mixture was extracted with ethyl acetate. The organic layer was washed, dried over and concentrated under reduced pressure. The residue was

purified by recrystallization from the mixture of AcOEt-hexane to give the title compound (80 mg) having the following physical data.

TLC : Rf 0.32 (MeOH : CH_2CI_2 = 15 : 85); NMR (DMSO-d₆) : δ 12.74 (1H, brs), 10.61 (1H, s), 10.40 (1H, s), 7.95 (2H, d), 7.85-7.71 (5H, m), 7.64-7.35 (5H, m).

Example 2(a)-2(bb)

10 [0104] The title compounds having the following physical data were obtained by the same procedure of Reference Example 1~Reference Example 3 and Examples 1 and 2.

Example 2(a)

3-(2-phenylsulfonylaminobenzoylamino)benzoic acid

[0105]

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TLC : Rf 0.57 (CHCl₃ : MeOH : AcOH= 100 : 10 : 1); NMR (DMSO-d₆) : δ 13.01 (1H, brs), 10.66 (1H, brs), 10.50 (1H, brs), 8.32 (1H, brs), 7.89 (1H, d), 7.76 (4H, m), 7.51 (6H, m), 7.23 (1H, m).

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Example 2(b)

3-(2-phenylsulfonylamino-5-chlorob nzoylamino)benzoic acid

[0106]

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10 СООН 15

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TLC : Rf 0.26 (MeOH : $CHCl_3 = 15 : 85$);

NMR (CDCl₃: DMSO-d₆=1:1): δ 12.70 (1H, brs), 10.69 (1H, s), 10.44 (1H, s), 8.27 (1H, t), 7.95-7.69 (5H, m), 7.59-

7.36 (6H, m).

25

Example 2(c)

4-(2-phenylsulfonylaminobenzoylamino)benzoic acid

30 [0107]

35

COOH

45

40

TLC: Rf 0.50 (CHCl3: MeOH: AcOH= 100: 10: 1);

NMR (DMSO-d₆) : δ 12.76 (1H, brs), 10.57 (1H, s), 10.49 (1H, s), 7.95 (2H, d), 7.77 (5H, m), 7.28-7.62 (5H, m),

7.24 (1H, m).

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Example 2(d)

4-[2-(4-chlorophenyl)sulfonylamino-5-chlorobenzoylamino]benzoic acid

⁵ [0108]

10 CI NH SO2

20

25

TLC: Rf 0.27 (MeOH: $CHCl_3 = 15:85$);

NMR (DMSO-d₆): δ 12.70 (1H, br s), 10.59 (1H, s), 10.30 (1H, s), 7.95 (2H, d), 7.83-7.66 (5H, m), 7.62-7.47 (3H, m), 7.34 (1H, d).

Example 2(e)

4-[2-(4-chlorophenylsulfonylamino)-4-chlorobenzoylamino]benzoic acid

[0109]

35

CI NH SO₂

45

40

 50 TLC : Rf 0.69 (CHCl₃ : MeOH : AcOH= 17 : 2 : 1); NMR (CDCl₃+DMSO-d₆) : δ 10.9-10.3 (1H, br), 10.3-9.9 (1H, br), 7.84 (2H, d), 7.7-7.5 (5H, m), 7.45 (1H, s-like), 7.17 (2H, d), 7.0-6.9 (1H, m).

Example 2(f)

4-[2-(4-chlorophenylsulfonylamino)-6-chlorobenzoylamino]benzoic acid

⁵ [0110]

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CI ON COOH

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TLC: Rf 0.67 (CHCl3: MeOH: AcOH= 17:2:1);

NMR: δ 9.64 (1H, s-like), 7.8-7.7 (2H, m), 7.5-7.3 (4H, m), 7.1-6.9 (5H, m).

Example 2(a)

4-[2-(4-chlorophenylsulfonylamino)-3-chlorobenzoylamino]benzoic acid

³⁰ [0111]

35

40

ON NH CI SO2

45

TLC: Rf 0.32 (CHCl₃: MeOH = 9:1);

NMR (DMSO-d₆): δ 12.8-12.6 (1H, br), 10.7-10.5 (1H, br), 10.12 (1H, s), 7.89 (2H, d), 7.7-7.5 (6H, m), 7.5-7.3 (3H, m).

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Example 2(h)

4-[2-(2-chlorophenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid

[0112]

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TLC : Rf 0.16 (CHCl₃ : MeOH = 9 : 1);

NMR (DMSO-d₆): δ 12.78 (1H, br), 10.80 (2H, br), 8.08-8.03 (1H, m),7.95 (2H, d), 7.88 (1H, d), 7.80 (2H, d), 7.66-

7.46 (4H, m), 7.38 (1H, d).

Example 2(i)

4-[2-(3-chlorophenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid

[0113]

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TLC: Rf 0.15 (CHCl₃: MeOH = 9:1);

NMR (DMSO-d₆): δ 12.76 (1H, br), 10.62 (1H, brs), 10.36 (1H, brs), 7.92 (2H, d), 7.77-7.73 (4H, m), 7.67-7.44 (4H,

m), 7.28 (1H, d).

55

Example 2(i)

4-[2-(4-chlorophenylsulfonylamino)-5-fluorobenzoylamino]benzoic acid

[0114]

10

5

F NH SO2 CI

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TLC : Rf 0.28 (MeOH : CHCl₃ = 15 : 85);

NMR (DMSO-d₆): δ 12.78 (1H, brs), 10.50 (1H, s), 10.09 (1H, s), 7.95 (2H, d), 7.75 (2H, d), 7.68-7.26 (7H, m).

Example 2(k)

4-[2-(4-chlorophenylsulfonylamino)-5-bromobenzoylamino]benzoic acid

[0115]

35

30

Br NH SO₂

45

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TLC: Rf 0.28 (MeOH: CHCl₃ = 15:85);

NMR (DMSO- d_6): δ 12.74 (1H, brs), 10.61 (1H, s), 10.33 (1H, s), 7.95 (2H, d), 7.89 (1H, d), 7.81-7.65 (5H, m), 7.53 (2H, d), 7.29 (1H, d).

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Example 2(I)

4-[2-(4-chlorophenylsulfonylamino)-5-methoxybenzoylamino]benzoic acid

[0116]

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TLC: Rf 0.30 (MeOH: $CHCl_3 = 15:85$);

NMR (DMSO-d₆): 8 12.77 (1H, brs), 10.39 (1H, s), 9.79 (1H, s), 7.94 (2H, d), 7.73 (2H, d), 7.59 (2H, d), 7.43 (2H, d), 7.25-7.15 (2H, m), 7.09 (1H, dd).

Example 2(m)

4-[2-(4-bromophenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid

[0117]

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СООН

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50 TLC : Rf 0.27 (CHCl₃ : MeOH = 9 : 1);

NMR (DMSO-d₆): δ 12.74 (1H, br), 10.55 (1H, brs), 10.27 (1H, brs), 7.92 (2H, d), 7.75-7.71 (3H, m), 7.66-7.51 (5H,

m), 7.31 (1H, d).

Example 2(n)

4-[2-(4-methylphenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid

[0118]

COOH 10 15

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TLC : Rf 0.30 (CHCl₃ : MeOH = 9:1);

NMR (DMSO-d₆): δ 12.76 (1H, br), 10.56 (1H, brs), 10.23 (1H, brs), 7.93 (2H, d), 7.77-7.73 (3H, m), 7.60-7.51 (3H,

m), 7.36 (1H, d), 7.23 (2H, d), 2.24 (3H, s).

Example 2(o)

4-[2-(4-methoxyphenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid

[0119]

СООН

45

TLC: Rf 0.29 (CHCl3: MeOH = 9:1);

NMR (DMSO-d₆): δ 12.76 (1H, br), 10.57 (1H, brs), 10.16 (1H, brs), 7.93 (2H, d), 7.77-7.73 (3H, m), 7.62 (2H, d),

7.59-7.52 (1H, m), 7.37 (1H, d), 6.93 (2H, d), 3.70 (3H, s).

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Example 2(p)

4-[2-(4-nitrophenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid

5 [0120]

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TLC : Rf 0.10 (CHCl₃ : MeOH = 9 : 1);

NMR (DMSO-d₆): δ 12.71 (1H, br), 10.55-10.35 (2H, br), 8.19 (2H, d), 7.93-7.86 (4H, m), 7.71-7.64 (3H, m), 7.58-7.52 (1H, m), 7.32 (1H, d).

Example 2(q)

4-[2-(2,4-dichlorophenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid

[0121]

35

40

CI NH CI SO2

45

TLC : Rf 0.22 (CHCl $_3$: MeOH = 9 : 1); NMR (DMSO-d $_6$) : δ 12.50 (1H, br), 10.73 (2H, br), 7.99-7.91 (3H, m), 7.85 (1H, d-like), 7.79-7.71 (3H, m), 7.58-7.51 (2H, m), 7.36 (1H, d).

55

Example 2(r)

4-[2-(4-butylphenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid

5 [0122]

CI NH SO2

TLC : Rf 0.33 (CHCl₃ : MeOH = 9 : 1);

NMR (DMSO-d₆): δ 12.72 (1H, br), 10.55 (1H, brs), 10.24 (1H, s), 7.92 (2H, d), 7.78-7.72 (3H, m), 7.60 (2H, d), 7.57-7.51 (1H, m), 7.37 (1H, d), 7.24 (2H, d), 2.54-2.49 (2H, m), 1.48-1.33 (2H, m), 1.29-1.11 (2H, m), 0.82 (3H, t).

Example 2(s)

4-[2-(4-chlorophenylsulfonylamino)benzoylamino]benzoic acid

30 [0123]

20

25

35

O
N
N
NH
SO
2
CI

45

TLC : Rf 0.30 (AcOEt : hexane : AcOH= 7 : 16 : 1); NMR (DMSO-d₆) : δ 13.00-12.60 (1H, brs), 10.55 (1H, brs), 10.38 (1H, brs), 7.95 (2H, d), 7.78 (2H, d), 7.74 (1H, m), 7.72 (2H, d), 7.51 (2H, d), 7.50 (1H, m), 7.40-7.24 (2H, m).

50

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Example 2(t)

4-(2-phenylsulfonylamino-5-fluorobenzoylamino)benzoic acid

[0124]

10

15

COOH

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TLC : Rf 0.23 (CHCl₃ : MeOH = 9:1);

NMR (DMSO- d_6): δ 12.70 (1H, br), 10.52 (1H, br), 10.13 (1H, br), 7.92 (2H, d), 7.74 (2H, d), 7.68-7.64 (2H, m),

COOH

7.59-7.27 (6H, m)

Example 2(u)

4-(2-phenylsulfonylamino-4-fluorobenzoylamino)benzoic acid

[0125]

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40

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TLC: Rf 0.20 (CHCl3: MeOH = 9:1);

NMR (DMSO-d₆) : δ 12.81 (1H, br), 10.85 (1H, br), 10.60 (1H, br), 7.95-7.74 (7H, m), 7.63-7.46 (3H, m), 7.19-7.02 (2H, m).

50

Exampl 2(v)

4-[2-(4-chlorophenylsulfonylamino)-4-fluorobenzoylamino]benzoic acid

5 [0126]

10

F NH SO₂ CI

20

25

15

TLC : Rf 0.22 (CHCl $_3$: MeOH = 9 : 1); NMR (DMSO-d $_6$) : δ 12.28 (1H, br), 10.75 (1H, br), 10.58 (1H, br), 7.95-7.72 (7H, m), 7.53 (2H, d), 7.19-7.08 (2H, m).

Example 2(w)

4-[2-(4-fluorophenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid

30 [0127]

35

40

CI NH SO2

45

TLC : Rf 0.26 (CHCl₃ : MeOH = 9 : 1); NMR (DMSO-d₆) : δ 12.75 (1H, br), 10.58 (1H, br), 10.27 (1H, brs), 7.93 (2H, d), 7.80-7.72 (5H, m), 7.54 (1H, dd), 7.34-7.22 (3H, m).

50

Example 2(x)

4-[2-(4-trifluoromethylphenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid

[0128]

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15

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25

TLC : Rf 0.26 (CHCl₃ : MeOH = 9:1);

NMR (DMSO-d₆) : δ 12.70 (1H, br), 10.56 (1H, br), 10.41 (1H, br), 7.92-7.68 (9H, m), 7.54 (1H, dd-like), 7.31 (1H, br), 10.56 (1H, br), 10.41 (1H, br), 1

d).

Example 2(y)

4-(2-phenylsulfonylamino-5-chlorobenzoylaminomethyl)benzoic acid

[0129]

35

40

45

TLC: Rf 0.45 (MeOH: $CHCl_3 = 1:4$);

NMR (DMSO- d_6): δ 12.90 (1H, s), 11.47 (1H, s), 9.46 (1H, t), 7.94 (2H, d), 7.86 (1H, d), 7.77-7.36 (9H, m), 4.48

(1H, d).

55

Example 2(z)

4-[2-(2-phenylvinyl)sulfonylamino-5-chlorobenzoylamino]benzoic acid

5 [0130]

10

20

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TLC : Rf 0.43 (CHCl₃ : MeOH = 9 : 1);

NMR (CD3OD): 87.98 (2H, d), 7.83 (1H, d), 7.72 (2H, d), 7.63 (1H, d), 7.53 (1H, dd), 7.5-7.2 (6H, m), 7.01 (1H, d).

25 Example 2(aa)

4-[2-(2-phenylethyl)sulfonylamino-5-chlorobenzoylamino]benzoic acid

[0131]

30

35

CI NH O₂S

45

40

TLC : Rf 0.27 (CHCl₃ : MeOH = 9 : 1); NMR (DMSO-d₆) : δ 12.75 (1H, br), 10.78 (1H, brs), 10.05 (1H, s), 7.95-7.79 (5H, m), 7.63-7.53 (2H, m), 7.24-7.10 (5H, m), 3.53-3.45 (2H, m), 2.99-2.91 (2H, m).

50

Example 2(bb)

4-[2-(4-chlorophenylsulfonylamino)-5-nitrobenzoylamino]benzoic acid

[0132]

5

10

15

O₂N COOH
NH
O₂S
CI

20

25

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35

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TLC: Rf 0.32 (AcOEt: hexane: AcOH= 4:12:1);

NMR (DMSO-d₆): δ 12.50-10.00 (2H, brs), 8.66 (1H, d), 8.36-8.24 (1H, dd), 8.05-7.87 (4H, m), 7.80 (2H, d), 7.68-7.55 (3H, m).

Example 3

4-[2-(4-hydroxyphenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid

[0133]

CI NH O2S OH

45

[0134] To a mixture solution of methyl 4-[2-(4-pivaroyloxyphenylsulfonylamino)-5-chlorobenzoylamino]benzoate (214 mg; prepared by the same procedure as Reference Examples 1, 2 and 3 and Example 1.) in MeOH-THF (8 ml + 3 ml), 2N NaOH aqueous solution (2 ml) was added The mixture was stirred for one day at 60°C. To the reaction solution, HCl was added. The mixture was extracted with ethyl acetate. The organic layer was washed, dried over and purified by recrystallization from the mixture solvent of MeOH-AcOEt-hexane to give the title compound (105 mg) having the following physical data.

TLC: Rf 0.42 (CHCl₃: MeOH: AcOH= 45:4:1);
NMR (DMSO-d₆): δ 13.0-12.6 (1H, br), 10.64 (1H, s-like), 10.50 (1H, s-like), 10.21 (1H, s), 7.95 (2H, d), 7.9-7.7 (3H, m), 7.6-7.3 (4H, m), 6.76 (2H, d).

Refer nce Exampl 4

Methyl 4-[2-(2-nitro-5-chlorophenyl)-(EZ)-vinyl]benzoate

5 **[0135]**

10

15

30

50

CI NO2

[0136] To a solution of 4-methoxycarbonylphenylmethyltriphenylphosphine bromide (4.83 g) in THF (20 ml), potassium t-butoxide (600 mg) was added. The mixture was stirred for 1 hour at room temperature. To the reaction solution, 2-nitro-5-chlorobenzaldehyde (742 mg) was added at 0°C. The mixture was stirred for 30 minutes at room temperature. The reaction mixture was poured into diluted HCl. The mixture was extracted with hexane-AcOEt. The organic layer was washed, dried over and concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (hexane-AcOEt) and recrystallization from the mixture solvent of hexane-AcOEt to give the title compound (680 mg) having the following physical data.

TLC: Rf 0.44 (hexane: AcOEt = 4:1).

Reference Example 5

Methyl 4-[2-(2-amino-5-chlorophenyl)-(E)-vinyl]benzoate and methyl 4-[2-(2-amino-5-chlorophenyl)-(Z)-vinyl]benzoate [0137]

[0138] To a solution of methyl 4-[2-(2-nitro-5-chlorophenyl)-(EZ)-vinyl]benzoate (525 mg; prepared in Reference Example 4.) in THF (4 ml), water (1.5 ml), 2N HCl and reduced iron (554 mg) were added. The mixture was stirred overnight at room temperature. Further, to the mixture, 2N HCl (0.2 ml) and reduced iron powder (330 mg) were added. The mixture was stirred for 3 days. The reaction mixture was diluted with ethyl acetate and filtrated. The filtrate was washed, dried over and concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (ether-hexane-AcOEt) to give the title compound having the following physical data.

(E) type compound

[0139]

5 TLC: Rf 0.37 (AcOEt: benzene = 5:95).

(Z) type compound

[0140]

10

TLC: Rf 0.41 (AcOEt: benzene = 5:95).

Example 4

Methyl 4-[2-[2-(4-chlorophenylsulfonylamino)-5-chlorophenyl]-(E)-vinyl]benzoate

[0141]

CI COOMe

NH

O₂S

30

35 [0142] To methyl 4-[2-(2-amino-5-chlorophenyl)-(E)-vinyl]benzoate (130 mg; prepared in Reference Example 5.) in methylene chloride (3 ml), pyridine (0.073 μl) and p-chlorobenzenesulfonylchloride (114 mg) were added. The mixture was stirred overnight at room temperature. The reaction mixture was poured into diluted HCl and extracted with ethyl acetate. The organic layer was washed, dried over and concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (AcOEt-hexane) to give the title compound (205 mg) having the following physical data.

TLC : Rf 0.15 (AcOEt : benzene = 4 : 96);
NMR : δ 8.02 (2H, d), 7.63 (2H, d), 7.51 (1H, s), 7.41-7.30 (4H, m), 7.26-7.22 (2H, m), 6.91 (1H, d), 6.81 (1H, d),

6.63 (1H, s), 3.95 (3H, s).

50

45

Example 4(a)

Methyl 4-[2-[2-(4-chlorophenylsulfonylamino)-5-chlorophenyl]-(Z)-vinyl]benzoate

[0143]

CI COOME
O2S
CI

20 [0144] By using Z type compound prepared in Reference Example 5, the title compound having the following physical data was obtained by the same procedure as Example 4.

TLC: Rf 0.23 (AcOEt: benzene = 4:96);
NMR: \$7.82 (2H, d), 7.57 (2H, d), 7.46 (1H, d), 7.33 (2H, d), 7.24 (1H, dd), 7.06 (1H, d), 6.99 (2H, d), 6.72 (1H, d), 6.48 (1H, s), 6.20 (1H, d), 3.90 (3H, s).

Example 5

4-[2-[2-(4-chlorophenylsulfonylamino)-5-chlorophenyl]-(E)-vinyl]benzoic acid

[0145]

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30

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40

CI NH O₂S CI

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[0146] By using methyl 4-[2-[2-(4-chlorophenylsulfonylamino)-5-chlorophenyl]-(E)-vinyl]benzoate (190 mg; prepared in Example 4.), the title compound (168 mg) having the following physical data was obtained by the same procedure as Example 2.

TLC : Rf 0.36 (MeOH : CHCl₃ = 15 : 85); NMR (DMSO-d₆) : δ 10.11 (1H, brs), 7.96 (2H, d), 7.80 (1H, d), 7.59 (2H, d), 7.52-.7.41 (4H, m), 7.36 (1H, dd), 7.20 (1H, d), 7.15 (1H, d), 7.08 (1H, d).

Example 5(a)

4-[2-[2-(4-chlorophenylsulfonylamino)-5-chlorophenyl]-(Z)-vinyl]benzoic acid

5 [0147]

CI NH COOH

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10

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[0148] By using methyl 4-[2-[2-(4-chlorophenylsulfonylamino)-5-chlorophenyl]-(Z)-vinyl]benzoate prepared in Example 4(a), the title compound having the following physical data was obtained by the same procedure as Example 2.

TLC : Rf 0.46 (MeOH : CHCl₃ = 15 : 85);

NMR (DMSO- d_6) : δ 10.05 (1H, brs), 7.79-7.67 (4H, m), 7.55 (2H, d),7.30 (1H, dd), 7.15 (1H, d), 7.00 (1H, d), 6.91 (1H, d), 6.64 (2H, s).

Example 6

4-[2-[2-(4-chlorophenyl)sulfonylamino-5-chlorophenyl]ethyl]benzoic acid

[0149]

35

CI NH O₂S

45

40

[0150] To a solution of 4-[2-[2-(4-chlorophenyl)sulfonylamino-5-chlorophenyl]vinyl]benzoic acid (54 mg; prepared in Example 5.) in THF (4 ml), platinum oxide hydrate (3 mg) was added. The mixture was stirred for 2 hours at room temperature in a stream of hydrogen. The reaction mixture was filtered and the filtrate was concentrated under the reduced pressure. To the residue, methylene chloride was added. The mixture was stirred. The precipitate was collected by filter to give the title compound (46 mg) having the following physical data.

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TLC : Rf 0.42 (MeOH : $CHCl_3 = 15 : 85$); NMR (DMSO-d₆) : δ 12.75 (H, s), 9.88 (1H, s), 7.84 (2H, d), 7.72-7.57 (4H, m), 7.32 (1H, d), 7.23 (2H, d), 7.18 (1H, dd), 6.88 (1H, d).

Refer nce Example 6

Methyl 4-(2-trifluoroacetylamino-5-chlorophenoxymethyl)benzoate

[0151]

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CI COOME

NH

OCF3

[0152] To a solution of 2-trifluoroacetylamino-5-chlorophenol (350 mg) and methyl 4-bromomethylbenzoate (435 mg) in DMF (3 ml), potassium carbonate (263 mg) was added at room temperature. The mixture was stirred for 1.5 hours at 60°C. After the termination of reaction, the reaction mixture was poured into diluted HCl and extracted with ethyl acetate. The organic layer was washed, dried over and concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (AcOEt-benzene) to give the title compound (353 mg) having the following physical data.

TLC: Rf 0.44 (AcOEt: benzene = 5:95).

30 Reference Example 7

Methyl 4-(2-amino-5-chlorophenoxymethyl)benzoate

[0153]

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CI COOMe

[0154] To a solution of methyl 4-(2-trifluoroacetylamino-5-chlorophenoxymethyl)benzoate (300 mg; prepared in Reference Example 6.) in mixture of THF-MeOH (4 ml + 10 ml), a solution of sodium carbonate (440 mg) in water (2 ml) was added. The solution was stirred for 8 hours at 60°C and overnight at room temperature. The reaction mixture was poured into diluted HCl and extracted with ethyl acetate. The organic layer was washed, dried over and concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (AcOEt-benzene) to give the title compound (194 mg) having the following physical data.

TLC: Rf 0.27 (AcOEt: benzene = 5:95).

Example 7

Methyl 4-[2-(4-chlorophenylsulfonylamino)-5-chlorophenoxymethyl]benzoate

[0155]

CI COOMe

NH

O₂S

CI

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[0156] By using methyl 4-(2-amino-5-chlorophenoxymethyl)benzoate (165 mg; prepared in Reference Example 7.), the title compound (259 mg) having the following physical data was obtained by the same procedure as Example 4.

TLC: Rf 0.30 (AcOEt: benzene = 5:95);

NMR : δ 8.06 (2H, d), 7.59 (2H, d), 7.53 (1H, d), 7.34 (2H, d), 7.18 (2H, d), 6.96 (1H, dd), 6.82 (1H, brs), 6.76 (1H, d), 4.89 (2H, s), 3.96 (3H, s).

Example 7(a)

Methyl 4-(2-phenylsulfonylamino-4-chlorophenoxymethyl)benzoate

[0157]

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CI NH:

O2S

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[0158] By using 2-trifluoroacetylamino-4-chlorophenol, the title compound having the following physical data was obtained by the same procedure as Reference Example 6-Reference Example 7-Example 4-Example 2.

TLC: Rf 0.37 (hexane: AcOEt = 2:1);

NMR : δ 8.01 (2H, d, J=8.4Hz), 7.75 (2H, m), 7.63 (1H, d, J=2.4Hz), 7.56 (1H, m), 7.43 (2H, m), 7.15 (2H, d, J=8.4Hz), 6.69 (1H, brs), 6.97 (1H, dd, J=2.4, 8.8Hz), 6.63 (1H, d, J=8.8Hz), 4.92 (2H, s), 3.94 (3H, s).

Example 8

4-[2-(4-chlorophenylsulfonylamino)-5-chlorophenoxymethyl]benzoic acid

[0159]

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1 COOH

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[0160] By using methyl 4-[2-(4-chlorophenylsulfonylamino)-5-chlorophenoxymethyl]benzoate (210 mg; prepared in Example 7.), the title compound (197 mg) having the following physical data was obtained by the same procedure as 25 Example 2.

TLC: Rf 0.43 (MeOH: CHCl₃ = 15:85); NMR (DMSO-d₆): δ 9.89 (1H, br s), 7.93 (2H, d), 7.60 (2H, d), 7.42 (2H, d), 7.34 (2H, d), 7.29 (1H, d), 7.06 (1H, d), 7.06 (1H, d), 7.06 (1H, d), 7.06 (1H, d), 7.07 (1H, d), 7.08 (1H, d), 7.88 d), 7.01 (1H, dd), 4.98 (2 H, s).

Example 8(a)-8(c)

[0161] The title compounds having the following physical data were obtained by the same procedure as Reference Examples 6, 7 and Examples 7 and 8.

Example 8(a)

4-(2-phenylsulfonylamino-5-chlorophenoxymethyl)benzoic acid

[0162]

СООН 45

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TLC: Rf 0.39 (MeOH: $CHCl_3 = 2:8$); NMR (DMSO- d_6): δ 12.98 (1H, s), 9.78 (1H, s), 7.92 (2H, d), 7.65 (2H, d), 7.55 (1H, t), 7.41 (2H, t), 7.37 (2H, d),

7.28 (1H, d), 7.04 (1H, dz), 6.98 (1H, dd), 4.98 (2H, s).

Example 8(b)

4-(2-phenylsulfonylamino-4-chlorophenoxymethyl)benzoic acid

[0163]

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CI NH O₂S

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TLC : Rf 0.40 (MeOH : $CHCl_3 = 2:8$);

NMR (DMSO- d_6) : δ 12.98 (1H, brs), 9.94 (1H, s), 7.90 (2H, d), 7.70 (2H, d), 7.58 (1H, t), 7.44 (2H,), 7.36 (2H, d), 7.28 (1H, d), 7.15 (1H, dd), 6.94 (1H, d), 4.97 (2H, s).

Example 8(c)

4-[2-(4-chlorophenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid

[0164]

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CI NH O₂S

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TLC: Rf 0.40 (MeOH: CHCl3 = 2:8);

NMR (DMSO-d₆): δ 12.93 (1H, s), 10.02 (1H, s), 7.88 (2H, d), 7.61 (2H, d), 7.42 (2H, d), 7.35-7.22 (3H, m), 7.17 (1H, dd), 6.93 (1H, d), 4.94 (2H, s).

Reference Example 8

O-mesyl-2-nitro-5-chlorobenzyl alcohol

5 [0165]

CI ON NO2

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[0166] A solution of 2-nitro-5-chlorobenzyl alcohol (400 mg) in methylene chloride (6 ml) was cooled by salt-ice. To this solution, triethylamine(0.6 ml) and mesylchloride (0.25 ml) were added. The mixture was stirred for 15 minutes. To the reaction mixture, water was added. The mixture was extracted with ethyl acetate. The organic layer was washed, dried over and concentrated under the reduced pressure to give the title compound (600 mg) having the following physical data.

TLC: Rf 0.36 (hexane: AcOEt = 2:1).

25 Reference Example 9

Methyl 4-(2-nitro-5-chlorophenylmethoxy)benzoate

[0167]

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CI COOMe

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[0168] To a solution of O-mesyl-2-nitro-5-chlorobenzyl alcohol (600 mg; prepared in Reference Example 8.) in acetone (10 ml), methyl 4-hydroxybenzoate (425 mg) and potassium carbonate (900 mg) were added. The mixture was stirred for 1 hour. To the reaction mixture, acetone (10 ml) was added. The mixture was stirred for 22 hours and filtered.
The filtrate was concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (hexane-AcOEt) to give the title compound (463 mg) having the following physical data.

TLC: Rf 0.26 (hexane: AcOEt = 2:1).

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Reference Example 10

Methyl 4-(2-amino-5-chlorophenylmethoxy)benzoate

[0169]

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[0170] A mixture of methyl 4-(2-nitro-5-chlorophenylmethoxy)benzoate (460 mg; prepared in Reference Example 9.),
THF (10 ml), water (3 ml), 1N HCl (0.4 ml) and iron powder (500 mg) was stirred for 13 hours. The reaction mixture was filtered. The filtrate was washed, dried over and concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (hexane-AcOEt) to give the title compound (419 mg) having the following physical data.

TLC: Rf 0.23 (hexane: AcOEt = 4:1).

Example 9

Methyl 4-[2-(4-chlorophenylsulfonylamino)-5-chlorophenylmethoxy]benzoate

[0171]

CI COOMe

NH

O₂S

45

[0172] To a solution of methyl 4-(2-amino-5-chlorophenylmethoxy)benzoate (450 mg; prepared in Reference Example 10.) in methylene chloride (4 ml), pyridine (0.24 ml) and 4-chlorobenzenesulfonylchloride (380 mg) were added. The mixture was stirred for 21 hour. To the reaction mixture, water was added. The mixture was extracted with ethyl acetate. The organic layer was washed, dried over and concentrated under the reduced pressure. The residue was purified by recrystallization from hexane-AcOEt mixture solvent to give the title compound (310 mg) having the following physical data.

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TLC : Rf 0.45 (benzene : AcOEt = 9 : 1); NMR : δ 8.01 (2H, d), 7.62 (2H, d), 7.40 (2H, d), 7.32-7.26 (3H, m), 7.11 (1H, brs), 6.90 (2H, d), 4.80 (2H, s), 3.90 (3H, s).

Example 10

4-[2-(4-chlorophenylsulfonylamino)-5-chlorophenylmethoxy]benzoic acid

⁵ [0173]

CI COOH

NH

O₂S

Ci

20

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15

[0174] By using methyl 4-[2-(4-chlorophenylsulfonylamino)-5-chlorophenylmethoxy]benzoate (300 mg; prepared in Example 9.), the title compound (187 mg) having the following physical data was obtained by the same procedure as Example 2.

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TLC: Rf 0.51 (AcOEt);

NMR (DMSO- d_6) : δ 10.2-10.0 (1H, br), 7.90 (2H, d), 7.69 (2H, d), 7.61 (2H, d), 7.49 (1H, d), 7.36 (1H, dd), 7.01 (1H, d), 6.92 (2H, d), 5.02 (2H, s).

Reference Example 11

2-phenylsulfonylamino-5-chloro-1-nitrobenzene

[0175]

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[0176] To a solution of 2-nitro-4-chloroanline (500 mg) and pyridine (2.1 ml in methylene chloride (10 ml), benzenesul-fonylchloride (1.2 ml) was added dropwise at 0°C under an atmosphere of argon. The reaction mixture was stirred for 3 days at room temperature. To the reaction mixture, water was added. The mixture was extracted with ethyl acetate. The organic layer was washed, dried over and concentrated under the reduced pressure. The reside was recrystallized from AcOEt-hexane mixture solvent to give the by-product. The mother liquor was concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (AcOEt-hexane) and recrystallized from AcOEt-hexane mixture solvent to give the title compound (175 mg) having the following physical data.

TLC: Rf 0.37 (AcOEt: hexane = 1:5).

Reference Example 12

2-phenylsulfonylamino-5-chloroaniline

[0177]

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CI NH2 O2 S

[0178] To a solution of 2-phenylsulfonylamino-5-chloro-1-nitrobenzene (172 mg; prepared in Reference Example 11.) in acetic acid (4 ml), reduced iron powder (154 mg) was added at room temperature under an atmosphere of argon. The suspension was stirred for 2 hours at 120°C. The reaction suspension was diluted with ethyl acetate and filtered. The filtrate was concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (AcOEt-hexane) to give the title compound (92 mg) having the following physical data.

TLC: Rf 0.34 (AcOEt: hexane = 1:2).

Example 11

Methyl 4-(2-phenylsulfonylamino-5-chlorophenylaminocarbonyl)benzoate

30 [0179]

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[0180] To a solution of 2-phenylsulfonylamino-5-chloroaniline (90 mg; prepared in Reference Example 12.) and pyridine (0.05 ml) in methylene chloride (5 ml), 4-methoxycarbonylbenzoic acid chloride (70 mg) was added at room temperature in a stream of argon. The mixture was stirred for 6 hours. After the termination of reaction, water was added to the reaction mixture. The mixture was extracted with ethyl acetate. The organic layer was washed, dried over and concentrated under the reduced pressure. The residue was purified by the recrystallization from AcOEt-hexane mixture solvent to give the title compound (112 mg) having the following physical data.

TLC: Rf 0.55 (AcOEt: hexane = 1:1);

NMR (CDCl $_3$ +DMSO-d $_6$) : δ 9.41 (1H, brs), 8.93 (1H, brs), 8.22 (1H, d), 8.15 (2H, d), 7.98 (2H, d), 7.72-7.62 (2H, m), 7.58-7.45 (1H, m), 7.44-7.32 (2H, m), 6.96 (1H, dd), 6.82 (1H, d).

Example 12

4-(2-phenylsulfonylamino-5-chlorophenylaminocarbonyl)benzoic acid

5 **[018**1]

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CI H NHO COOH

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[0182] By using methyl 4-(2-phenylsulfonylamino-5-chlorophenylaminocarbonyl)benzoate (110 mg; prepared in Example 11.), the title compound (107 mg) having the following physical data was obtained by the same procedure as Example 2.

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TLC : Rf 0.36 (AcOEt : hexane : AcOH= 8 : 10 : 1); NMR (DMSO-d₆) : δ 13.00 (1H, brs), 9.80 (1H, brs), 9.65 (1H, s), 8.09 (2H, d), 7.87 (2H, d), 7.81 (1H, d), 7.65-7.50 (3H, m), 7.40 (2H, t), 7.22 (1H, dd), 7.14 (1H, d).

30 Reference Example 13

2-nitro-5-chlorobenzoic acid chloride

[0183]

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CICOCI

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[0184] A solution of 2-nitro-5-chlorobenzoic acid (200 mg) in sulfonylchloride (20 ml) was stirred for 4 hours at 99°C in a stream of argon. After leaving to cool, the solution was concentrated under the reduced pressure to give the title compound.

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Reference Example 14

1-(2-nitro-5-chlorobenzoyl)-1-(4-methoxycarbonylphenyl)methylidene triphenylphosphoran

5 [0185]

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[0186] To a solution of 4-methoxycarbonylbenzyltriphenylphosphonium bromide (1.17 g) in THF (8 ml), potassium t-butoxide (246 mg) was added in a stream of argon. The mixture was stirred for 30 minutes. A solution of 2-nitro-5-chlorobenzoic acid chloride (prepared in Reference Example 13.) in THF (4 ml) was added dropwise to the reaction solution. The mixture was stirred for 3 hours at room temperature. The reaction mixture was quenched by adding saturated aqueous ammonium chloride and extracted with chloroform. The organic layer was washed, dried over and concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (CHCl₃-MeOH) to give the title compound (619 mg) having the following physical data.

TLC: Rf 0.26 (CHCl₃: MeOH = 100:1).

30 Reference Example 15

Methyl 4-[2-(2-nitro-5-chlorophenyl)ethynyl]benzoate

[0187]

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[0188] A solution of 1-(2-nitro-5-chlorobenzoyl)-1-(4-methoxycarbonylphenyl)methylidene triphenylphosphoran (513 mg; prepared in Reference Example 14.) in o-dichlorobenzene (10 ml) was refluxed for 9 hours at 180°C in a stream of argon. The reaction mixture was concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (hexane-AcOEt) to give the title compound (189 mg) having the following physical data.

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TLC: Rf 0.39 (hexane: AcOEt = 7:1).

Reference Example 16

Methyl 4-[2-(2-amino-5-chlorophenyl)ethynyl]benzoate

5 [0189]

CI NH₂

[0190] To a solution of methyl 4-[2-(2-nitro-5-chlorophenyl)ethynyl]benzoate (180 mg; prepared in Reference Example 15.) in acetic acid (3.6 ml), reduced iron powder (160 mg) was added. The mixture was refluxed for 30 minutes and filtered. The filtrate was concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (hexane-AcOEt) to give the title compound (144 mg) having the following physical data. TLC: Rf 0.25 (hexane: AcOEt = 5:1).

Example 13

Methyl 4-[2-[2-(4-chlorophenylsulfonylamino)-5-chlorophenyl]ethynyl]benzoate

30 [0191]

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CI NH O₂S CI

50 [0192] To a solution of methyl 4-[2-(2-amino-5-chlorophenyl)ethynyl]benzoate (136 mg; prepared in Reference Example 16.) in methylene chloride (2 ml), pyridine (77 μl) and 4-chlorobenzenesulfonyl chloride (106 mg) were added at 0°C under an atmosphere of argon. The mixture was stirred for 24 hours at room temperature. The reaction mixture was diluted with ethyl acetate, washed, dried over and concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (hexane-AcOEt) to give the title compound (207 mg) having the following physical data.

TLC: Rf 0.50 (hexane: AcOEt = 3:1);

NMR: 8 8.07 (2H, d), 7.67 (2H, d), 7.58 (1H, d), 7.49 (2H, d), 7.39 (1H, d), 7.34 (2H, d), 7.32 (1H, dd), 7.07 (1H,

brs), 3.96 (3H, s).

Example 14

4-[2-[2-(4-chlorophenylsulfonylamino)-5-chlorophenyl]ethynyl]benzoic acid

[0193]

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CI NH O₂S

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[0194] By using methyl 4-[2-[2-(4-chlorophenylsulfonylamino)-5-chlorophenyl]ethynyl]benzoate (199 mg; prepared in Example 13.), the title compound (181 mg) having the following physical data was obtained by the same procedure as Example 2.

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TLC : Rf 0.43 (CHCl $_3$: MeOH : AcOH= 100 : 5 : 1); NMR (DMSO-d $_6$) : δ 13.16 (1H, brs), 10.32 (1H, brs), 8.00 (2H, d), 7.65 (2H, d), 7.59 (1H, d), 7.57 (2H, d), 7.50 (1H, dd), 7.43 (2H, d), 7.35 (1H, d).

Reference Example 17

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Methyl 4-(2-amino-5-trifluoromethylphenoxymethyl)benzoate

[0195]

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[0196] By using 2-nitro-5-trifluoromethylphenol, the title compound having the following physical data was obtained by the same procedure as Reference Example 6-> Reference Example 12.

TLC: Rf 0.33 (hexane: AcOEt = 3:1).

Example 15

Methyl 4-(2-phenylsulfonylamino-5-trifluoromethylphenoxymethyl)benzoate

[0197]

COOMe

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[0198] By using methyl 4-(2-amino-5-trifluoromethylphenoxymethyl)benzoate (prepared in Reference Example 17.), the title compound having the following physical data was obtained by the same procedure as Example 7.

TLC: Rf 0.76 (benzene: acetone = 9:1);

NMR: δ 8.05 (2H, d, J=8.2Hz), 7.77 (2H, m), 7.69 (1H, d, J=8.6Hz), 7.58 (1H, m), 7.45 (2H, m), 7.25 (3H, m), 7.18 (1H, m), 6.99 (1H, m), 5.02 (2H, s), 3.95 (3H, s).

Example 16

4-(2-phenylsulfonylamino-5-trifluoromethylphenoxymethyl)benzoic acid

[0199]

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COOH

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By using methyl 4-(2-phenylsulfonylamino-5-trifluoromethylphenoxymethyl)benzoate (prepared in Example 15.), the title compound having the following physical data was obtained by the same procedure as Example 2.

TLC: Rf 0.52 (CHCl3: MeOH: AcOH= 100:5:1);

NMR (DMSO-d₆): δ 12.95 (1H, brd), 10.10 (1H, brd), 7.93 (2H, d, J=8.0Hz), 7.75 (2H, m), 7.59 (1H, m), 7.40-7.53

55 (5H, m), 7.27 (2H, m), 5.14 (2H, s).

Example 17

Methyl 4-[2-(N-isopropyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoate

[0201]

СООМе

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[0202] To a solution of methyl 4-(2-phenylsulfonylamino-4-chlorophenoxymethyl)benzoate (402 mg; prepared in Example 7(a).) in DMF (4 ml), potassium carbonate (256 mg) and isopropyl iodide (185 ml) were added. The mixture was stirred overnight at room temperature and for 9 hours at 50°C. To the reaction solution, iced water and 2N HCl were 25 added. The mixture was extracted with ethyl acetate. The organic layer was washed, dried over, concentrated after filtration, solidified with ethanol and washed to give the title compound (411 mg) having the following physical data.

TLC: Rf 0.59 (hexane: AcOEt = 2:1);

NMR : δ 8.05 (2H, d, J=8.8Hz), 7.83-7.79 (2H, m), 7.55-7.26 (6H, m), 7.08 (1H, d, J=2.8Hz), 6.89 (1H, d, J=8.8Hz),5.04 (2H, s), 4.36 (1H, sept, J=6.8Hz), 3.93 (3H, s), 1.05 (6H, d, J=6.8Hz).

Example 17(1)-(4)

[0203] By using the corresponding compounds, the title compounds having the following physical data were obtained by the same procedure as Reference Example 6→Reference Example 7→Example 7→Example 17 or Reference Example 8→Reference Example 9→Reference Example 10→Example 9→Example 17.

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Example 17(1)

Methyl 4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoate

[0204]

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TLC: Rf 0.55 (hexane: AcOEt = 2:1);

NMR : δ 8.07 (2H, d, J=8.4Hz), 7.79 (2H, m), 7.44-7.55 (3H, m), 7.32-7.43 (2H, m), 7.18-7.29 (3H, m), 5.10 (2H, s), 4.38 (1H, sept, J=6.6Hz), 3.94 (3H, s), 1.05 (6H, d, J=6.6Hz).

Example 17(2)

Methyl 4-[2-(N-isopropyl-phenylsulfonylamino)-5-methylphenoxymethyl]benzoate

30 [0205]

Me O COOMe

45

TLC: Rf 0.48 (hexane: AcOEt = 2:1);

NMR: δ 8.04 (2H, d, J=8.4Hz), 7.80 (2H, m), 7.41-7.52 (3H, m), 7.28-7.39 (2H, m), 6.97 (1H, d, J=8.6Hz), 6.73-6.80 (2H, m), 5.00 (2H, s), 4.38 (1H, sept, J=7.0Hz), 3.93 (3H, s), 2.35 (3H, s), 1.05 (6H, d, J=7.0Hz).

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Example 17(3)

Methyl 4-[2-(N-isopropyl-phenylsulfonylamino)-5-chlorophenoxymethyl]benzoate

5 [0206]

CIOOMe

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TLC: Rf 0.30 (hexane: AcOEt = 4:1);

 $NMR: \delta~8.06~(2H,~d,~J=8.2Hz),~7.78~(2H,~d,~J=7.2Hz),~7.25-7.48~(5H,~m),~6.85-7.05~(3H,~m),~5.02~(2H,~s),~4.37~(1H,~s),~2.54-1.01~(2H,~d,~J=8.2Hz),~2.54-1.01~(2H,~d,~J=8.2Hz),~2.54-1.01~(2H,~d,~J=8.2Hz),~2.54-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8.2Hz),~2.24-1.01~(2H,~d,~J=8$

sept, J=6.4Hz), 3.94 (3H, s), 1.04 (6H, d, J=6.4Hz).

Example 17(4)

Methyl 4-[2-(N-isopropyl-2-furanylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamate

30 [0207]

F₃C COOMe

45

TLC: Rf 0.39 (benzene: AcOEt = 19:1);

NMR: δ 7.71 (1H, d, J=16Hz), 7.59-7.45 (5H, m), 7.23-7.20 (3H, m), 6.94-6.92 (1H, m), 6.50-6.42 (2H, m), 5.12

(2H, s), 4.5-4.4 (1H, m), 3.82 (3H, s), 1.09 (6H, dd, J=6.5, 2Hz).

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Example 18

4-[2-(N-isopropyl-phenylsulfonylamino-4-chlorophenoxymethyl]benzoic acid

[0208]

CI O₂S COOH

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[0209] By using methyl 4-[2-(N-isopropyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoate (prepared in Example 17.), the title compound having the following physical data was obtained by the same procedure as Example 2.

TLC: Rf 0.43 (CHCl₃: MeOH: H₂O = 9:1:0.1);
NMB (DMSO-d₂): \$ 12.90 (1H, br) 7.94 (2H, d, J

NMR (DMSO- d_6): δ 12.90 (1H, br), 7.94 (2H, d, J=8.4Hz), 7.78 (2H, d, J=8.4Hz), 7.66-7.45 (6H, m), 7.23 (1H, d, J=8.4Hz), 7.07 (1H, d, J=2.4Hz), 5.13 (2H, s), 4.20 (1H, sept, J=6.6Hz), 0.99 and 0.96 (each 3H, each d, J=6.6Hz).

Example 18(1)-18(128)

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[0210] By using the corresponding compounds, the title compounds having the following physical data were obtained by the same procedure as Reference Example 6→Reference Example 7→Example 17→Example 2 or Reference Example 8→Reference Example 9→Reference Example 10→Example 17→Example 2.

35 <u>Example 18(1)</u>

4-[2-(N-carboxymethyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid

[0211]

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CI COOH

O2S

O2S

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TLC : Rf 0.20 (CHCl $_3$: MeOH : H $_2$ O = 7 : 3 : 0.3); NMR (DMSO-d $_6$) : δ 12.93 (2H, br), 7.88 (2H, d, J=8.4Hz), 7.63-7.37 (7H, m), 7.16-7.06 (3H, m), 4.88 (2H, s), 4.31 (2H, s).

Example 18(2)

4-[2-[N-(2-hydroxyethyl)-phenylsulfonylamino]-4-chlorophenoxymethyl]benzoic acid

5 [0212]

СООН

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TLC: Rf 0.26 (CHCl₃: MeOH: $H_2O = 9:1:0.1$);

NMR (DMSO-d₆): δ 12.71 (1H, br), 7.88 (2H, d, J=8.4Hz), 7.63-7.32 (7H, m), 7.19-7.08 (3H, m), 4.89 (2H, brs),

4.71 (1H, br), 3.86-3.40 (4H, m).

Example 18(3)

4-[2-(N-methyl-phenylsulfonylamino)-4-trifluoromethylphenoxymethyl]benzoic acid

[0213]

COOH

45

TLC: Rf 0.31 (CHCl₃: MeOH: $H_2O = 9:1:0.1$); NMR (DMSO-d₆): δ 12.90 (1H, br), 7.90 (2H, d, J=8.4Hz), 7.76-7.70 (1H, dd-like), 7.64-7.43 (6H, m), 7.31 (1H, d, J=8.4Hz), 7.23 (2H, d, J=8.4Hz), 5.05 (2H, s), 3.18 (3H, s).

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Example 18(4)

4-[2-[N-(2-hydroxyethyl)-phenylsulfonylamino]-4-trifluoromethylphenoxymethyl]benzoic acid

5 [0214]

F₃C OOH
O₂S O

TLC: Rf 0.24 (CHCl₃: MeOH: $H_2O = 9:1:0.1$); NMR (DMSO-d₆): δ 12.51 (1H, br), 7.89 (2H, d, J=8.4Hz), 7.74 (1H, dd, J=2.2 and 8.4Hz), 7.62-7.37 (6H, m), 7.28 (1H, d, J=8.4Hz), 7.20 (2H, d, J=8.4Hz), 5.00 (2H, brs), 4.70 (1H, br), 3.66-3.28 (4H, m).

Example 18(5)

30 4-[2-[N-(2-hydroxyethyl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid

[0215]

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TLC : Rf 0.40 (CHCl₃ : MeOH : AcOH= 100 : 5 : 1); NMR (DMSO-d₆) : δ 12.96 (1H, brd), 7.89 (2H, d, J=8.4Hz), 7.61 (2H, m), 7.34-7.58 (6H, m), 7.20 (2H, d, J=8.4Hz), 5.05 (1H, brs), 4.67 (1H, m), 3.60 (2H, m), 3.42 (2H, m).

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EP 0 947 500 A1

Example 18(6)

4-[2-(N-methyl-phenylsulfonylamino)-5-chlorophenoxymethyl]benzoic acid

5 [0216]

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СООН

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TLC: Rf 0.36 (CHCl₃: MeOH: $H_2O = 9:1:0.1$);

NMR (DMSO-d₆) : δ 12.63 (1H, br), 7.89 (2H, d, J=8.4Hz), 7.64-7.41 (5H, m), 7.25-7.19 (4H, m), 7.05 (1H, dd,

J=2.2 and 8.4Hz), 4.98 (2H, s), 3.12 (3H, s).

Example 18(7)

4-[2-[N-(2-hydroxyethyl)-phenylsulfonylamino]-5-chlorophenoxymethyl]benzoic acid

[0217] 30

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COOH

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TLC: Rf 0.27 (CHCl₃: MeOH: $H_2O = 9:1:0.1$);

NMR (DMSO-d₆) : δ 12.88 (1H, br), 7.89 (2H, d, J=8.4Hz), 7.62-7.36 (5H, m), 7.29-7.17 (4H, m), 7.06 (1H, dd,

J=2.2 and 8.4Hz), 4.95 (2H, brs), 4.68 (1H, br), 3.66-3.24 (4H, br).

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Example 18(8)

4-[2-(N-methyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

5 **[0218]**

F₃C COOH
O₂S

20

TLC: Rf 0.46 (CHCl3: MeOH: AcOH= 100:5:1);

NMR: δ 8.08 (2H, d, J=8.0Hz), 7.68 (2H, m), 7.12-7.53 (8H, m), 4.93 (2H, s), 3.24 (3H, s).

25 Example 18(9)

4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0219]

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F₃C OOH

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TLC: Rf 0.44 (CHCl3: MeOH: AcOH= 100:5:1);

 $NMR: \delta \ 8.15 \ (2H, d, J=8.6Hz), \ 7.81 \ (2H, m), \ 7.52 \ (3H, m), \ 7.38 \ (2H, m), \ 7.24 \ (3H, m), \ 5.13 \ (2H, s), \ 4.40 \ (1H, sept, m), \ 5.13 \ (2H, s), \ 4.40 \ (1H, sept, m), \ 5.13 \ (2H, s), \ 4.40 \ (1H, sept, m), \ 5.13 \ (2H, s), \ 4.40 \ (1H, sept, m), \ 5.13 \ (2H, s), \ 4.40 \ (1H, sept, m), \ 5.13 \ (2H, s), \ 4.40 \ (1H, sept, m), \ 5.13 \ (2H, s), \ 4.40 \ (1H, sept, m), \ 5.13 \ (2H, s), \ 4.40 \ (1H, sept, m), \ 5.13 \ (2H, s), \ 4.40 \ (1H, sept, m), \ 5.13 \ (2H, s), \ 4.40 \ (1H, sept, m), \ 5.13 \ (2H, s), \ 4.40 \ (1H, sept, m), \ 5.13 \ (2H, s), \ 4.40 \ (1H, sept, m), \ 5.13 \ (2H, s), \ 5.13 \ (2H$

J=6.8Hz), 1.06 (6H, d, J=6.8Hz).

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Example 18(10)

 $\hbox{$4$-[2-(N-isopropyl-phenylsulfonylamino)-5-chlorophenoxymethyl]} benzoic\ acid$

[0220]

5

10 CI COOH

O2S

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TLC: Rf 0.35 (CHCl₃: MeOH: $H_2O = 9:1:0.1$);

NMR (DMSO- d_6): δ 12.96 (1H, br), 7.95 (2H, d, J=8.2Hz), 7.78-7.74 (2H, m), 7.65-7.43 (5H, m), 7.32 (1H, s), 7.07 (2H, s), 5.21 and 5.07 (each 1H, each d, J=15.6Hz), 4.21 (1H, sept-like), 0.94 (6H, d, J=6.8Hz).

Example 18(11)

4-[2-(N-isopropyl-phenylsulfonylamino)-4-trifluoromethylphenoxymethyl]benzoic acid

[0221]

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TLC: Rf 0.30 (CHCl₃: MeOH: $H_2O = 9:1:0.1$);

NMR (DMSO-d₆): δ 13.03 (1H, br), 7.95 (2H, d, J=8.2Hz), 7.84-7.74 (3H, m), 7.67-7.39 (6H, m), 7.25 (1H, d, J=2.4Hz), 5.28 and 5.21 (each 1H, each d, J=16.6Hz), 4.26 (1H, sept-like), 0.98 and 0.97 (each 3H, each d, J=6.6Hz).

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Example 18(12)

4-[2-[N-(2-methoxyethoxymethyl)-phenylsulfonylamino]-4-chlorophenoxymethyl]benzoic acid

[0222]

CI OME

O2S

OME

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TLC: Rf 0.40 (CHCl₃: MeOH: $H_2O = 9:1:0.1$);

 $NMR \; (DMSO-d_6): \delta \; 12.98 \; (1H,\,br), \; 7.91 \; (2H,\,d,\,J=8.2Hz), \; 7.66-7.52 \; (3H,\,m), \; 7.45-7.38 \; (3H,\,m), \; 7.26-7.22 \; (3H,\,m), \; 7.45-7.38 \; (3H,\,m), \; 7.26-7.22 \; (3H,\,m), \; 7.45-7.38 \; (3H,\,m),$

7.10 (1H, d, J=8.2Hz), 5.06 (2H, brs), 4.92 (2H, brs), 3.68-3.63 (2H, t-like), 3.42-3.37 (2H, t-like), 3.21 (3H, s).

Example 18(13)

 $\hbox{$4$-[2-[N-(2-methoxyethyl)-phenylsulfonylamino]-4-chlorophenoxymethyl] benzoic acid$

[0223]

CI OME
O2S
O2S

45

TLC: Rf 0.25 (CHCl₃: MeOH: $H_2O = 9:1:0.1$);

NMR (DMSO-d₆) : δ 12.92 (1H, br), 7.88 (2H, d, J=8.2Hz), 7.64-7.39 (6H, m), 7.22-7.10 (4H, m), 4.91 (2H, brs),

3.69 (2H, br), 3.38-3.33 (2H, m), 3.13 (3H, s)

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Example 18(14)

 $\hbox{$4$-[2-[N-[2-(2-methoxyethoxy)ethyl]-phenylsulfonylamino]-4-chlorophenoxymethyl] benzoic acid$

[0224]

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COOH OMe O₂S

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TLC: Rf 0.29 (CHCl₃: MeOH: $H_2O = 9:1:0.1$);

J=8.2Hz), 7.11 (1H, d, J=8.2Hz), 4.92 (2H, brs), 3.69 (2H, br), 3.47-3.28 (6H, m), 3.19 (3H, s).

Example 18(15)

4-[2-(N-ethyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid

[0225] 30

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TLC: Rf 0.51 (CHCl3: MeOH = 9:1);

NMR : δ 8.08 (2H, d, J=8.2Hz), 7.8-7.6 (2H, m), 7.5-7.2 (7H, m), 6.81 (1H, d, J=9.4Hz), 4.88 (2H, s), 3.67 (2H, q,

J=7.0Hz), 1.11 (3H, t, J=7.0Hz).

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СООН

Example 18(16)

4-[2-(N-propyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid

5 **[0226**]

10 CI N O 2S

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TLC : Rf 0.50 (CHCl₃ : MeOH = 9:1);

NMR : δ 8.08 (2H, d, J=8.4Hz), 7.7-7.6 (2H, m), 7.5-7.2 (7H, m), 6.80 (1H, d, J=9.6Hz), 4.85 (2H, s), 3.6-3.5 (2H, m), 1.6-1.4 (2H, m), 0.89 (3H, t, J=7.2Hz).

Example 18(17)

4-[2-(N-butyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid

30 [0227]

CI NO2S

45

TLC : Rf 0.53 (CHCl₃ : MeOH = 9:1);

NMR: δ 8.08 (2H, d, J=8.4Hz), 7.7-7.6 (2H, m), 7.5-7.2 (7H, m), 6.80 (1H, d, J=9.4Hz), 4.86 (2H, s), 3.7-3.5 (2H, m), 1.5-1.2 (4H, m), 0.85 (3H, t, J=7.0Hz).

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Example 18(18)

4-[2-(N-pentyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid

5 [0228]

10 CI COOH
O25

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TLC : Rf 0.56 (CHCl₃ : MeOH = 9:1);

NMR: δ 8.08 (2H, d, J=8.2Hz), 7.7-7.6 (2H, m), 7.5-7.2 (7H, m), 6.8-6.7 (1H, m), 4.86 (2H, s), 3.6-3.5 (2H, m), 1.5-

1.2 (6H, m), 0.9-0.8 (3H, m).

Example 18(19)

4-[2-(N-hexyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid

30 **[0229]**

CI O2S

45

TLC: Rf 0.58 (CHCl3: MeOH = 9:1);

NMR: 8 8.08 (2H, d, J=8.6Hz), 7.7-7.6 (2H, m), 7.5-7.2 (7H, m), 6.9-6.8 (1H, m), 4.86 (2H, s), 3.6-3.5 (2H, m), 1.5-1.1 (2H, m), 2.2.2 (2H, m), 2.5.2 (2H, m

1.1 (8H, m), 0.9-0.8 (3H, m).

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СООН

Example 18(20)

4-[2-(N-benzyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid

5 **[0230]**

10 CI NO O2 S

20

TLC : Rf 0.60 (CHCl₃ : MeOH = 9 : 1);

NMR: δ 8.09 (2H, d, J=8.6Hz), 7.8-7.7 (2H, m), 7.6-7.3 (3H, m), 7.3-7.1 (9H, m), 6.71 (1H, d, J=8.8Hz), 4.82 (2H,

s), 4.78 (2H, s).

Example 18(21)

4-[2-(N-isopropyl-phenylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

30 [0231]

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Me O COOH

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TLC: Rf 0.50 (CHCl3: MeOH: AcOH= 100: 5:1);

NMR: 88.13 (2H, d, J=8.2Hz), 7.82 (2H, m), 7.49 (3H, m), 7.36 (2H, m), 6.98 (1H, d, J=8.6Hz), 6.77 (2H, m), 5.05

(2H, s), 4.40 (1H, sept, J=6.6Hz), 2.36 (3H, s), 1.05 (6H, d, J=6.6Hz).

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Example 18(22)

4-[2-(N-methyl-phenylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

[0232]

10 Me COOH

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TLC: Rf 0.56 (AcOEt: hexane: AcOH= 9:10:1);

NMR (DMSO-d₆) : δ 12.96 (1H, brs), 7.89 (2H, d, J=8.5Hz), 7.67-7.40 (5H, m), 7.23 (2H, d, J=8.0Hz), 7.06 (1H, d, J=8.0Hz), 6.93 (1H, d, J=8.0Hz), 4.93 (2H, s), 3.12 (3H, s), 2.30 (3H, s).

Example 18(23)

4-[2-[N-(2-hydroxyethyl)-phenylsulfonylamino]-5-methylphenoxymethyl]benzoic acid

[0233]

45

TLC: Rf 0.27 (AcOEt: hexane: AcOH= 9:10:1);

NMR (DMSO-d₆) : δ 12.95 (1H, brs), 7.87 (2H, d, J=8.5Hz), 7.55-7.32 (5H, m), 7.20 (2H, d, J=8.5Hz), 7.08 (1H, d, J=8.0Hz), 6.91 (1H, s), 6.77 (1H, d, J=8.0Hz), 4.89 (2H, brs), 4.63 (1H, t, J=4.0Hz), 3.50-3.20 (4H, m), 2.29 (3H, s).

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Example 18(24)

4-[2-[N-(prop-2-enyl)-phenylsulfonylamino]-4-chlorophenoxymethyl]benzoic acid

5 **[0234]**

10 CI N COOH

TLC : Rf 0.54 (CHCl₃ : MeOH = 9 : 1);

NMR : δ 8.08 (2H, d, J=8.0Hz), 7.8-7.6 (2H, m), 7.6-7.2 (7H, m), 6.78 (1H, d, J=9.4Hz), 5.9-5.6 (1H, m), 5.2-5.0 (2H, m), 4.86 (2H, s), 4.3-4.2 (2H, m).

Example 18(25)

4-[2-(N-cyclopentyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid

30 **[0235]**

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35 CI N O₂S

TLC: Rf 0.47 (CHCl3: MeOH = 9:1);

NMR: δ 8.13 (2H, d, J=8.4Hz), 7.9-7.8 (2H, m), 7.6-7.2 (6H, m), 7.07 (1H, d, J=2.6Hz), 6.88 (1H, d, J=8.8Hz), 5.1-5.0 (2H, m), 4.5-4.3 (1H, m), 2.0-1.7 (2H, m), 1.6-1.2 (6H, m).

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Example 18(26)

4-[2-[N-(2-methoxyethyl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid

5 [0236]

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TLC : Rf 0.46 (CHCl $_3$: MeOH : AcOH= 100 : 5 : 1); NMR : δ 8.07 (2H, d, J=8.4Hz), 7.66 (2H, m), 7.18-7.53 (7H, m), 7.12 (1H, m), 4.90 (2H, s), 3.81 (2H, m), 3.51 (2H, t, J=6.0Hz), 3.24 (3H, s).

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Example 18(27)

4-[2-(N-ethyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

⁰ [0237]

F₃C COOH

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TLC : Rf 0.43 (CHCl₃ : MeOH = 9 : 1); NMR : δ 8.09 (2H, d, J=8.4Hz), 7.7-7.6 (2H, m), 7.5-7.2 (7H, m), 7.15 (1H, d, J=1.6Hz), 4.94 (2H, s), 3.69 (2H, q, J=7.4Hz), 1.11 (3H, t, J=7.4Hz).

Example 18(28)

4-[2-(N-propyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

5 **[0238**]

F₃C COOH

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TLC: Rf 0.5 (CHCl₃: MeOH = 9:1);

NMR : δ 8.09 (2H, d, J=8.2Hz), 7.7-7.6 (2H, m), 7.5-7.2 (7H, m), 7.14 (1H, s), 4.92 (2H, s), 3.59 (2H, t, J=7.4Hz),

1.6-1.4 (2H, m), 0.88 (3H, t, J=7.4Hz).

Example 18(29)

4-[2-(N-isobutyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

30 [0239]

F₃C COOH

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TLC : Rf 0.53 (CHCl₃ : MeOH = 9 : 1);

NMR : δ 8.10 (2H, d, J=8.4Hz), 7.7-7.6 (2H, m), 7.5-7.2 (7H, m), 7.11 (1H, d, J=1.6Hz), 5.0-4.8 (2H, m), 3.44 (2H,

d, J=7.4Hz), 1.7-1.5 (1H, m), 0.90 (6H, d, J=6.4Hz).

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Example 18(30)

4-[2-(N-cyclopentyl-phenylsulfonyamino)-5-trifluoromethylphenoxymethy]benzoic acid

5 [0240]

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TLC : Rf 0.54 (CHCl₃ : MeOH = 9 : 1);

NMR: δ 8.15 (2H, d, J=8.0Hz), 7.8-7.7 (2H, m), 7.6-7.3 (5H, m), 7.3-7.2 (3H, m), 5.2-5.0 (2H, m), 4.5-4.3 (1H, m),

2.0-1.8 (2H, m), 1.6-1.2 (6H, m).

Example 18(31)

4-[2-[N-(prop-2-enyl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid

30 [0241]

F₃C O COOH

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TLC: Rf 0.47 (CHCl3: MeOH = 9:1);

NMR: \$8.10 (2H, d, J=8.6Hz), 7.8-7.6 (2H, m), 7.6-7.2 (7H, m), 7.12 (1H, s), 5.9-5.6 (1H, m), 5.1-5.0 (2H, m), 4.93

(2H, s), 4.24 (2H, d, J=6.2Hz).

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Example 18(32)

4-[2-[N-(2-methylprop-2-enyl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid

[0242]

СООН 10 15

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TLC: Rf 0.48 (CHCl₃: MeOH = 9:1);

NMR: δ 8.10 (2H, d, J=8.4Hz), 7.7-7.6 (2H, m), 7.5-7.2 (7H, m), 7.10 (1H, s), 4.89 (2H, s), 4.71 (2H, d, J=12.0Hz),

4.20 (2H, s), 1.74 (3H, s).

Example 18(33)

4-[2-(N-isopropyl-4-methylphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0243]

COOH Me يز

45

TLC: Rf 0.60 (CHCl3: MeOH: AcOH= 100:5:1);

NMR: 88.14 (2H, d, J=8.4Hz), 7.68 (2H, d, J=8.2Hz), 7.52 (2H, d, J=8.2Hz), 7.19 (5H, m, arom), 5.14 (2H, s), 4.38

(1H, sept., J=6.8Hz), 2 38 (3H, s), 1.05 (6H, d, J=6.8Hz).

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Example 18(34)

4-[2-(N-isopropyl-4-fluorophenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

5 [0244]

F₃C COOH

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TLC: Rf 0.60 (CHCl3: MeOH: AcOH= 100:5:1);

NMR: 88.16 (2H, d, J=8.2Hz), 7.76 (2H, m, arom), 7.52 (2H, d, J=8.2Hz), 7.26 (3H, m, arom), 7.01 (2H, m, arom),

5.10 (2H, dd, J=11.8, 14.6Hz), 4.38 (1H, sept., J=6.4Hz), 1.09 (3H, d, J=6.4Hz), 1.07 (3H, d J=6.4Hz).

Example 18(35)

 $\hbox{$4$-[2-(N-isopropyl-4-methoxyphenyl sulfonyl amino)-5-trifluor omethyl phenoxymethyl] benzoic acid}$

[0245]

F₃C O COOH
O₂S O OMe

45

TLC: Rf 0.60 (CHCl3: MeOH: AcOH= 100: 5:1);

NMR: δ 8.15 (2H, d, J=8.2Hz), 7.72 (2H, d, J=8.8Hz), 7.53 (2H, d, J=8.2Hz), 7.18 (3H, m, arom), 6.81 (2H, d, J=9.2Hz), 5.14 (2H, s), 4.35 (1H, sept., J=6.4Hz), 3.83 (3H, s), 1.08 (3H, d, J=6.4Hz), 1.05 (3H, d, J=6.4Hz).

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Example 18(36)

4-[2-(N-isopropyl-phenylsulfonylamino)-5-chlorophenoxy]benzoic acid

5 [0246]

10 CI COOH
O₂S

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TLC: Rf 0.36 (CHCl₃: MeOH = 9:1);

NMR : δ 8.11 (2H, d, J=8.6Hz), 7.8-7.7 (2H, m), 7.6-7.3 (3H, m), 7.2-7.1 (2H, m), 7.02 (2H, d, J=8.6Hz), 6.92 (1H, d, J=2.0Hz), 4.6-4.4 (1H, m), 1.14 (3H, d, J=2.4Hz), 1.11 (3H, d, J=2.4Hz).

Example 18(37)

3-[2-(N-isopropyl-phenylsulfonylamino)-5-chlorophenoxy]cinnamic acid

30 [0247]

CI COOH

45

TLC : Rf 0.33 (CHCl₃ : MeOH = 9:1);

NMR: δ 7.9-7.8 (2H, m), 7.73 (1H, d, J=15.8Hz), 7.6-7.3 (5H, m), 7.2-7.0 (4H, m), 6.78 (1H, d, J=2.2Hz), 6.42 (1H, d, J=15.8Hz), 4.6-4.4 (1H, m), 1.17 (3H, d, J=6.8Hz), 1.13 (3H, d, J=6.8Hz).

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Example 18(38)

trans-4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]cyclohexanoic acid

[0248]

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TLC: Rf 0.53 (CHCl3: MeOH: AcOH= 100:5:1);

NMR : δ 7.81 (2H, m), 7.42-7.63 (3H, m), 7.10-7.24 (3H, m), 4.38 (1H, sept, J=6.8Hz), 3.79 (2H, m), 2.33 (1H, tt, J=3.8, 10.2Hz), 2.11 (2H, m), 1.93 (2H, m), 1.71 (1H, m), 1.50 (2H, m), 1.18 (2H, m), 1.07 (3H, d, J=6.8Hz), 1.02 (3H, d, J=6.8Hz).

Example 18(39)

4-[2-(N-isopropyl-phenylsulfonylamino)-5-chlorophenoxy]phenylacetic acid

[0249]

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TLC: Rf 0.43 (CHCl3: MeOH = 9:1);

NMR : δ 7.9-7.8 (2H, m), 7.6-7.4 (3H, m), 7.28 (2H, d, J=7.4Hz), 7.13 (1H, d, J=8.6Hz), 7.01 (1H, dd, J=2.2, 8.6Hz), 6.89 (2H, d, J=8.6Hz), 6.78 (1H, d, J=2.2Hz), 4.6-4.4 (1H, m), 3.66 (2H, s), 1.15 (3H, s), 1.12 (3H, s).

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Example 18(40)

4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

5 [0250]

F₃C COOH

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TLC : Rf 0.5 (CHCl₃ : MeOH = 9 : 1);

NMR: 87.9-7.8 (3H, m), 7.60 (2H, d, J=8.0Hz), 7.5-7.3 (5H, m), 7.3-7.2 (3H, m), 6.49 (1H, d, J=15.8Hz), 5.08 (2H,

s), 4.4-4.3 (1H, m), 1.05 (6H, d, J=6.6Hz).

Example 18(41)

30 3-[4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]phenyl]propionic acid

[0251]

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50 TLC: Rf 0.59 (CHCl₃: MeOH = 9:1);

NMR: δ 7.80 (2H, d, J=7.4Hz), 7.5-7.4 (1H, m), 7.4-7.2 (9H, m), 4.99 (2H, s), 4.4-4.2 (1H, m), 3.00 (2H, t, J=7.6Hz),

2.72 (2H, t, J=7.6Hz), 1.08 (3H, d, J=6.8Hz), 1.02 (3H, d, J=6.8Hz).

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Example 18(42)

3-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]phenylacetic acid

5 [0252]

10 F₃C СООН

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TLC : Rf 0.50 (CHCl₃ : MeOH = 9:1);

NMR : δ 7.8-7.7 (2H, m), 7.6-7.2 (10H, m), 5.05 (1H, d, J=11.0Hz), 4.98 (1H, d, J=11.0Hz), 4.4-4.2 (1H, m), 3.68 (2H, s), 1.06 (3H, d, J=6.6Hz), 1.03 (3H, d, J=6.6Hz).

Example 18(43)

4-[2-(N-isopropyl-4-ethoxyphenylsulfonylamino)-5-triflouromethylphenoxymethyl]benzoic acid

30 **[0253]**

F₃C COOH

O₂S OC₂H₅

45

TLC: Rf 0.44 (CHCl3: MeOH = 9:1);

NMR: δ 8.15 (2H, d, J=8.2Hz), 7.71 (2H, d, J=8.8Hz), 7.54 (2H, d, J=8.2Hz), 7.3-7.2 (3H, m), 6.78 (2H, d, J=8.8Hz), 5.14 (2H, s), 4.4-4.2 (1H, m), 4.03 (2H, q, J=7.0Hz), 1.44 (3H, t, J=7.0Hz), 1.08 (3H, d, J=7.0Hz), 1.04 (3H, d, J=7.0Hz).

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Example 18(44)

4-[2-(N-isobutyl-phenylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

5 **[0254]**

10 Me COOH

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TLC : Rf 0.47 (CHCl $_3$: MeOH : AcOH= 100 : 5 : 1); NMR : δ 8.07 (2H, d, J=8.2Hz), 7.63 (2H, m), 7.15-7.44 (6H, m), 6.79 (1H, m), 6.65 (1H, m), 4.80 (2H, m), 3.40 (2H, m), 2.33 (3H, s), 1.63 (1H, m), 0.90 (6H, d, J=6.4Hz).

Example 18(45)

4-[2-(N-isopropyl-phenylsulfonylamino)-5-fluorophenoxymethyl]benzoic acid

30 **[0255]**

FO₂S COOH

45

TLC : Rf 0.33 (CHCl₃ : MeOH = 20 : 1); NMR (DMSO-d₆) : δ 7.95 (2H, d, J=8.2Hz), 7.80 (2H, d, J=7.2Hz), 7.46-7.65 (5H, m), 7.08 (2H, m), 6.82 (1H, m), 5.14 (2H, bs), 4.20 (1H, sept, J=6.6Hz), 0.94 (6H, d, J=6.6Hz).

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Example 18(46)

4-[2-(N-isopropyl-phenylsulfonylamino)-5-methoxyphenoxymethyl]benzoic acid

[0256] 5

СООН 10 O₂S 15

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TLC: Rf 0.30 (CHCl3: MeOH = 20:1);

NMR (DMSO-d₆) : δ 7.95 (2H, d, J=8.2Hz), 7.73 (2H, d, J=7.2Hz), 7.42-7.68 (3H, m), 6.93 (2H, d, J=8.6Hz), 7.21 (1H, m), 6.56 (2H, dd, J=8.6Hz, J=2.8Hz), 5.11 (2H, bs), 4.20 (1H, sept, J=6.6Hz), 3.79 (3H, s), 0.94 (6H, d, J=6.6Hz).

Example 18(47)

4-[2-(N-propyl-phenylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

[0257]

СООН

45

TLC: Rf 0.38 (CHCl3: MeOH: AcOH= 100: 5:1);

NMR: δ 8.07 (2H, d, J=8.6Hz), 7.67 (2H, m), 7.15-7.45 (6H, m), 6.79 (1H, m), 6.68 (1H, m), 4.83 (2H, brs), 3.57 (2H, m), 2.34 (3H, s), 1.48 (2H, m), 0.88 (3H, t, J=7.4Hz).

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Example 18(48)

4-[2-[N-(prop-2-enyl)-phenylsulfonylamino]-5-methylphenoxymethyl]benzoic acid

[0258]

COOH 10

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TLC: Rf 0.39 (CHCl3: MeOH: AcOH= 100: 5:1);

NMR: 8 8.07 (2H, d, J=8.0Hz), 7.69 (2H, m), 7.13-7.48 (6H, m), 6.78 (1H, m), 6.66 (1H, m), 5.80 (1H, tdd, J=6.2,

10.2, 17.2Hz), 4.98-5.12 (2H, m), 4.84 (2H, brs), 4.23 (2H, m), 2.33 (3H, s).

Example 18(49)

4-[2-[N-(2-methylprop-2-enyl)-phenylsulfonylamino]-5-methylphenoxymethyl]benzoic acid

30 [0259]

COOH

45

TLC: Rf 0.37 (CHCl3: MeOH: AcOH= 100: 5:1);

NMR: 5 8.07 (2H, d, J=8.2Hz), 7.66 (2H, m), 7.16-7.47 (6H, m), 6.77 (1H, m), 6.64 (1H, m), 4.80 (2H, brs), 4.71

(2H, m), 4.20 (1H, brs), 2.32 (3H, s), 1.77 (3H, s).

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Example 18(50)

4-[2-(N-cyclopropylmethyl-phenylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

[0260]

10 Me COOH

NO 2S

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TLC: Rf 0.31 (CHCl3: MeOH: AcOH= 100:5:1);

NMR : δ 8.06 (2H, d, J=8.0Hz), 7.68 (2H, m), 7.18-7.44 (6H, m), 6.80 (1H, m), 6.68 (1H, m), 4.84 (2H, brs), 3.48 (2H, m), 2.34 (2H, m), 2.34

(2H, m), 2.34 (3H, s), 0.91 (1H, m), 0.38 (2H, m), 0.07 (2H, m).

Example 18(51)

4-[2-(N-propyl-phenylsulfonylamino)-5-chlorophenoxymethyl]benzoic acid

[0261]

CI COOH

45

TLC: Rf 0.32 (CHCl₃: MeOH = 20:1);

NMR : δ 8.07 (2H, d, J=7.8Hz), 7.64 (2H, d, J=6.8Hz), 7.10-7.41 (6H, m), 6.85-6.99 (2H, m), 4.82 (2H, bs), 3.55

(2H, t, J=6.8Hz), 1.35-1.52 (2H, m), 0.87 (3H, t, J=7.6Hz).

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Example 18(52)

4-[2-(N-isobutyl-phenylsulfonylamino)-5-chlorophenoxymethyl]benzoic acid

5 **[0262]**

10 CI COOH
O2S

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TLC : Rf 0.32 (CHCl₃ : MeOH = 20 : 1);

NMR : δ 8.04 (2H, d, J=7.8Hz), 7.54 (2H, d, J=7.4Hz), 7.10-7.41 (6H, m), 6.80-7.01 (2H, m), 4.58-4.95 (2H, bs), 3.34 (2H, d, J=7.0Hz), 1.46-1.65 (1H, m), 0.83 (6H, d, J=6.4Hz).

Example 18(53)

4-[2-[N-(prop-2-enyl)-phenylsulfonylamino]-5-chlorophenoxymethyl]benzoic acid

30 [0263]

CI COOH

45

TLC: Rf 0.30 (CHCl₃: MeOH = 20: 1);

NMR : δ 8.09 (2H, d, J=8.2Hz), 7.68 (2H, d, J=6.8Hz), 7.19-7.52 (6H, m), 6.87-7.01 (2H, m), 5.76 (1H, ddt, J=17.2Hz, 9.8Hz, 6.4Hz) 5.09 (1H, d, J=17.2Hz), 5.07 (1H, d, J=9.8Hz), 4.85 (2H, s), 4.21 (2H, d, J=6.4Hz).

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Example 18(54)

4-[2-[N-(2-methylprop-2-enyl)-phenylsulfonylamino]-5-chlorophenoxymethyl]benzoic acid

[0264]

10 CI COOH
O2S

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TLC: Rf 0.33 (CHCl₃: MeOH = 20:1);

NMR: 8 8.09 (2H, d, J=8.2Hz), 7.65 (2H, d, J=6.8Hz), 7.21-7.51 (6H, m), 6.83-7.00 (2H, m), 4.81 (2H, s), 4.74 (1H, s), 4.68 (1H, s), 4.75 (9H, s), 4.75 (9H,

s), 4.68 (1H, s), 4.18 (2H,s), 1.75 (3H, s).

Example 18(55)

4-[2-(N-cyclopropylmethyl-phenylsulfonylamino)-5-chlorophenoxymethyl]benzoic acid

30 [0265]

CI COOH

45

TLC: Rf 0.40 (CHCl₃: MeOH = 20:1);

NMR : δ 8.07 (2H, d, J=8.6Hz), 7.69 (2H, d, J=7.0Hz), 7.20-7.48 (6H, m), 6.85-7.09 (2H, m), 4.85(2H, s), 3.47 (2H,

bs), 0.85 (1H, m), 0.38 (2H, m), 0.06 (2H, m).

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Example 18(56)

5-[2-(N-isopropyl-phenylsulfonylamino)-5-methylphenoxymethyl]furan-2-carboxylic acid

5 **[0266]**

Me COOH

20 TLC : Rf 0.18 (CHCl₃ : MeOH = 9 : 1);

NMR : δ 7.82 (2H, m), 7.56-7.35 (3H, m), 7.31 (1H, d, J =3.5Hz), 6.97 (1H, d, J=8.5Hz), 6.83-6.75 (2H, m), 6.63 (1H, d, J=3.5Hz), 5.03 (1H, d, J=14Hz), 4.98 (1H, d, J=14Hz), 4.37 (1H, m), 2.37 (3H, s), 1.09-0.96 (6H, m).

25 Example 18(57)

4-[2-(N-methoxymethyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0267]

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F₃C O OMe O₂S

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TLC : Rf 0.45 (CHCl $_3$: MeOH : AcOH= 100 : 5 : 1); NMR : δ 8.09 (2H, d, J=8.0Hz), 7.65 (2H, m), 7.43-7.53 (2H, m), 7.20-7.40 (5H, m), 7.11 (1H, m), 5.09 (2H, s), 4.89 (2H, s), 3.44 (3H, s).

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Example 18(58)

4-[2-(N-isopropyl-2-thienylsulfonylamino)-5-chlorophenoxymethyl]benzoic acid

[0268]

5

10 CI COOH

O2S S

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TLC : Rf 0.34 (CHCl₃ : MeOH = 20 : 1);

NMR: 8 8.14 (2H, d, J=8.2Hz), 7.52-7.57 (4H, m), 6.98-7.03 (4H, m), 5.12 (2H, s), 4.55 (1H, sept, J=6.4Hz), 1.09

(6H, d, J=6.6Hz).

Example 18(59)

4-[2-(N-isopropyl-2-thienylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

30 **[0269**]

Me O COOH

45

TLC: Rf 0.39 (CHCl₃: MeOH = 20:1);

NMR: δ 8.13 (2H, d, J=8.2Hz),7.43-7.58 (4H, m), 6.97 (1H, m), 6.80 (2H, m), 5.12 (2H, s), 4.45 (1H, sept, J=6.4Hz),

1.09 (6H, d, J=6.6Hz).

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Example 18(60)

4-[2-(N-isopropyl-2-furanylsulfonylamino)-5-methylphenoxymethyl[benzoic acid

5 **[0270]**

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TLC: Rf 0.42 (CHCl3: MeOH: AcOH= 100:5:1);

NMR : δ 8.14 (2H, d, J=8.2Hz), 7.58 (2H, d, J=8.2Hz), 7.44 (1H, dd, J=0.8, 1.6Hz), 6.88-6.95 (2H, m), 6.72-6.82 (2H, m), 6.41 (1H, dd, J=1.6, 3.4Hz), 5.12 (2H, s), 4.51 (1H, sept, J=6.6Hz), 2.31 (3H, s), 1.12 (3H, d, J=6.6Hz), 1.10 (3H, d, J=6.6Hz).

Example 18(61)

4-[2-(N-isopropyl-2-furanylsulfonylamino)-5-chlorophenoxymethyl]benzoic acid

[0271]

35

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30

CI COOH

45

TLC: Rf 0.43 (CHCl3: MeOH: AcOH= 100: 5:1);

NMR : δ 8.16 (2H, d, J=8.4Hz), 7.57 (2H, d, J=8.4Hz), 7.45 (1H, dd, J=0.8, 1.6Hz), 6.95-7.04 (3H, m), 6.92 (1H, d, J=4.4Hz), 6.43 (1H, dd, J=1.8, 3.4Hz), 5.13 (2H, s), 4.49 (1H, sept, J=7.0Hz), 1.11 (3H, d, J=7.0Hz), 1.09 (3H, d, J=7.0Hz).

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СООН

Example 18(62)

4-[2-(N-isobutyl-phenylsulfonylamino)-4-methylphenoxymethyl]benzoic acid

5 [0272]

10 Me O₂S

20

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TLC: Rf 0.23 (hexane: AcOEt = 1:1);

NMR : δ 8.06 (2H, d, J=8Hz), 7.65-7.61 (2H, m), 7.6-7.4 (7H, m), 6.71 (1H, d, J=8Hz), 4.9-4.6 (2H, m), 3.5-3.4 (2H, m), 2.29 (3H, s), 1.63 (1H, sept., J=6.5 Hz), 0.91 (6H, d, J=6.5Hz).

Example 18(63)

4-[2-(N-isopropyl-phenylsulfonylamino)-4-methylphenoxymethyl]benzoic acid

[0273]

Me O₂S

45

TLC: Rf 0.22 (hexane: AcOEt = 1:1);

NMR: δ 8.12 (2H, d, J=8Hz), 7.86-7.81 (2H, m), 7.52-7.30 (5H, m), 7.15-7.10 (1H, m), 6.94 (1H, d, J=1.5Hz), 6.84 (1H, d, J=8Hz), 5.02 (2H, s), 4.37 (1H, sept., J=6.5 Hz), 2.28 (3H, s), 1.08 (6H, t, J=6.5 Hz).

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Example 18(64)

4-[2-[N-(prop-2-enyl)-phenylsulfonylamino]-4-methylphenoxymethyl]benzoic acid

5 **[0274]**

Me COOH

O2S

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TLC : Rf 0.43 (CHCl $_3$: MeOH : AcOH= 100 : 5 : 1); NMR (DMSO-d $_6$) : δ 7.89 (2H, d, J=8.2Hz), 7.63 (2H, m), 7.38-7.59 (3H, m), 7.23 (2H, d, J=8.2Hz), 7.12 (1H, dd, J=1.8, 8.4Hz), 6.98 (1H, d, J=1.8Hz), 6.94 (1H, d, J=8.6Hz), 5.71 (1H, tdd, J=6.4, 10.0, 17.2Hz), 4.97-5.13 (2H, m), 4.88 (2H, brs), 4.17 (2H, m), 2.22 (3H, s).

Example 18(65)

30 4-[2-(N-isopropyl-4-ethoxyphenylsulfonylamino)-5-chlorophenoxymethyl]benzoic acid

[0275]

40

CI COOH

O25

OC2H5

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TLC : Rf 0.33 (CHCl₃ : MeOH = 20 : 1);

NMR : δ 8.13 (2H, d, J=8.6Hz), 7.69 (2H, d, J=9.0Hz), 7.49 (2H, d, J=8.6Hz), 6.97-7.09 (3H, m), 6.76 (2H, d, J=9.0Hz), 5.06 (2H, s), 4.34 (1H, sept, J=6.6Hz), 4.02 (2H, q, J=7.2Hz), 1.43 (3H, t, J=7.0Hz), 1.06 (3H, d, J=6.6Hz), 1.03 (3H, d, J=6.6Hz).

Example 18(66)

4-[2-(N-isopropyi-4-ethoxyphenylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

5 [0276]

Me COOH

O2S

OC2H5

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TLC : Rf 0.29 (CHCl₃ : MeOH = 20 : 1);

NMR: δ 8.12 (2H, d, J=8.4Hz), 7.72 (2H, d, J=8.6Hz), 7.50 (2H, d, J=8.6Hz), 7.01 (1H, d, J=8.8Hz), 6.72-6.80 (4H, m), 5.07 (2H, s), 4.34 (1H, sept, J=6.6Hz), 4.01 (2H, q, J=7.0Hz), 2.36 (3H, s), 1.42 (3H, t, J=6.8Hz), 1.07 (3H, d, J=7.2Hz), 1.04 (3H, d, J=6.8Hz).

Example 18(67)

4-[2-(N-ethyl-phenylsulfonylamino)-4-methylphenoxymethyl]benzoic acid

[0277]

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Me O₂S

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TLC : Rf 0.33 (CHCl₃ : MeOH = 9:1);

NMR: δ 8.05 (2H, d, J=8.4Hz), 7.8-7.6 (2H, m), 7.4-7.2 (5H, m), 7.2-7.0 (2H, m), 6.75 (1H, d, J=8.4Hz), 4.82 (2H, s), 3.8-3.6 (2H, m), 2.30 (3H, s), 1.11 (3H, t, J=7.0Hz).

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Example 18(68)

4-[2-(N-propyl-phenylsulfonylamino)-4-methylphenoxymethyl]benzoic acid

5 **[0278]**

10 Me O₂S O₂S

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TLC: Rf 0.44 (CHCl3: MeOH = 9:1);

NMR : δ 8.05 (2H, d, J=8.0Hz), 7.7-7.6 (2H, m), 7.5-7.0 (7H, m), 6.74 (1H, d, J=8.4Hz), 4.80 (2H, s), 3.7-3.5 (2H, m), 2.29 (3H, s), 1.6-1.4 (2H, m), 0.89 (3H, t, J=7.4Hz).

Example 18(69)

4-[2-(N-butyl-phenylsulfonylamino)-4-methylphenoxymethyl]benzoic acid

30 [0279]

35 Me N COOH
O2S

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TLC : Rf 0.49 (CHCl₃ : MeOH = 9 : 1);

NMR: δ 8.05 (2H, d, J=8.2Hz), 7.7-7.6 (2H, m), 7.4-7.2 (5H, m), 7.2-7.0 (2H, m), 6.74 (1H, d, J=8.4Hz), 4.80 (2H, s), 3.7-3.5 (2H, m), 2.30 (3H, s), 1.6-1.2 (4H, m), 0.85 (3H, t, J=7.0Hz).

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Example 18(70)

4-[2-[N-(2-methylprop-2-enyl)-phenylsulfonylamino]-4-methylphenoxymethyl]benzoic acid

5 [0280]

COOH

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TLC: Rf 0.38 (CHCl3: MeOH = 9:1);

NMR: δ 8.06 (2H, d, J=8Hz), 7.65 (2H, m), 7.47-7.25 (3H, m), 7.19 (2H, d, J=8Hz), 7.13 (1H, d, J=2Hz), 7.04 (1H, dd, J=8 and 2Hz), 6.70 (1H, d, J=8Hz), 4.85-4.65 (4H, m), 4.21 (2H, s), 2.29 (3H, s), 1.78 (3H, s).

Example 18(71)

4-[2-(N-cyclopropylmethyl-phenylsulfonylamino)-4-methylphenoxymethyl]benzoic acid

[0281]

СООН

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TLC: Rf 0.40 (CHCl3: MeOH: AcOH= 100:5:1);

NMR (CD₃COCD₃): δ 7.99(2H, d, J=8.0Hz), 7.68 (2H, m), 7.26-7.57 (5H, m), 7.15 (2H, m), 6.96 (1H, d, J=8.8Hz), 4.93 (2H, brs), 3.52 (2H, brd, J=7.0Hz), 2.28 (3H, s), 0.90 (1H, m), 0.35 (2H, m), 0.06 (2H, m).

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Example 18(72)

4-[2-(N-isopropyl-propylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

5 [0282]

10 Me COOH

TLC: Rf 0.24 (CHCl₃: MeOH = 19:1);

NMR: δ 8.14 (2H, d, J=8.2Hz), 7.57 (2H, d, J=8.2Hz), 7.16 (1H, m), 6.82 (2H, m), 5.13 (2H, s), 4.33 (1H, m), 2.97 (2H, m), 2.36 (3H, s), 1.79 (2H, m), 1.23 (3H, d, J=6.6Hz), 1.09 (3H, d, J=6.6Hz), 0.85 (3H, t, J=7.4Hz).

Example 18(73)

25 4-[2-(N-isopropyl-pentylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

[0283]

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Me COOH

TLC : Rf 0.26 (CHCl₃ : MeOH = 19 : 1);

NMR: δ 8.15 (2H, d, J=8.0Hz), 7.56 (2H, d, J=8.0Hz), 7.14 (1H, m), 6.81 (2H, m), 5.12 (2H, s), 4.32 (1H, m), 2.97 (2H, m), 2.36 (3H, s), 1.77 (2H, m), 1.24 (3H, d, J=6.6Hz), 1.16 (4H, m), 1.09 (3H, d, J=6.6Hz), 1.12 (3H, d, J=6.6Hz), 0.83 (3H, t, J=6.4Hz).

Example 18(74)

4-[2-(N-benzyl-methylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

5 [0284]

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Me COOH

20 TLC: Rf 0.39 (CHCl₃: MeOH = 19:1);

NMR : δ 8.17 (2H, d, J=8.0Hz), 7.53 (2H, d, J=8.0Hz), 7.25 (5H, s), 6.98 (1H, m), 6.77 (2H, m), 5.17 (2H, s), 4.70 (2H, bs), 2.89 (3H, s), 2.30 (3H, s).

Example 18(75)

4-[2-(N-benzyl-propylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

[0285]

35 Me COOH

TLC: Rf 0.40 (CHCl₃: MeOH = 19:1);

NMR: 88.17 (2H, d, J=8.2Hz), 7.55 (2H, d, J=8.2Hz), 7.23 (5H, s), 6.98 (1H, m), 6.78 (2H, m), 5.16 (2H, s), 4.77

(2H, bs), 2.95 (2H, m), 2.29 (3H, s), 1.81 (2H, m), 0.85 (3H, t, J=7.6Hz).

Example 18(76)

4-[2-(N-isopropyl-cyclopentylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

[0286]

10 Me COOH

20 TLC : Rf 0.38 (CHCl₃ : MeOH : AcOH= 100 : 5 : 1);

NMR : δ 8.15 (2H, d, J=8.0Hz), 7.59 (2H, d, J=8.0Hz), 7.14 (1H, d, J=8.6Hz), 6.81 (2H, m), 5.12 (2H, s), 4.35 (1H, sept, J=6.6Hz), 3.51 (1H, m), 2.36 (3H, s), 1.85-2.15 (3H, m), 1.61-1.85 (3H, m), 1.34-1.61 (2H, m), 1.22 (3H, d, J=6.6Hz), 1.08 (3H, d, J=6.6Hz).

Example 18(77)

4-[2-(N-isobutyl-ethylsulfonylamino)-4-methylphenoxymethyl]benzoic acid

30 [0287]

35 Me N COOH

45 TLC: Rf 0.23 (hexane: AcOEt = 1:1);

NMR : δ 8.15 (2H, d, J=8Hz), 7.53 (2H, d, J=8Hz), 7.21 (1H, d, J=1.5Hz), 7.08 (1H, dd, J=8.5, 1.5Hz), 6.86 (1H, d, J=8.5Hz), 5.17 (2H, s), 3.46 (2H, d, J=7.5Hz), 2.97 (2H, q, J=7.5Hz), 2.30 (3H, s), 1.7-1 .5 (1H, m), 1.25 (3H, t, J=7.5Hz), 0.94-0.90 (6H, m).

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Example 18(78)

4-[2-(N-isobutyl-propylsulfonylamino)-4-methylphenoxymethyl]benzoic acid

5 [0288]

10 Me O₂S COOH

20 TLC: Rf 0.27 (hexane: AcOEt = 1:1);

NMR : δ 8.15 (2H, d, J=8Hz), 7.53 (2H, d, J=8Hz), 7.20 (1H, d, J=0.5Hz), 7.03 (1H, dd, J=8, 0.5Hz), 6.86 (1H, d, J=8Hz), 5.17 (2H, s), 3.44 (2H, d, J=7Hz), 2.94-2.86 (2H, m), 2.30 (3H, s), 1.9-1.6 (3H, m), 1.0-0.9(6H, m), 0.85 (3H, t, J=7Hz).

25 Example 18(79)

4-[2-(N-isobutyl-butylsulfonylamino)-4-methylphenoxymethyl]benzoic acid

[0289]

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Me O₂S COOH

45 TLC: Rf 0.37 (hexane: AcOEt = 1:1);

NMR : δ 8.15 (2H, d, J=8Hz), 7.53 (2H, d, J=8Hz), 7.20 (1H, d, J=0.5Hz), 7.08 (1H, dd, J=8.5, 0.5Hz), 6.86 (1H, d, J=8.5Hz), 5.16 (2H, s), 3.45 (2H, d, J=7Hz), 2.97-2.89 (2H, m), 2.30 (3H, s), 1.8-1.5 (3H, m), 1.3-1.1 (2H, m), 1.0-0.9(6H, m), 0.79 (3H, t, J=7Hz).

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Example 18(80)

4-[2-(N-isobutyl-propylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

5 **[0290**]

10 Me COOH
02S

TLC : Rf 0.25 (CHCl₃ : MeOH = 20 : 1);

NMR : δ 8.16 (2H, d, J=8.4Hz), 7.53 (2H, d, J=8.4Hz), 7.28 (1H, m), 6.82 (2H, m), 5.18 (2H, s), 3.41 (2H, d, J=7.0Hz), 2.89 (2H, m), 2.35 (3H, s), 1.78 (2H, m), 1.60 (1H, m), 0.90 (6H, d, J=7.0Hz), 0.84 (3H, t, 7.6Hz).

Example 18(81)

4-[2-[N-(prop-2-enyl)-propylsulfonylamino]-5-methylphenoxymethyl]benzoic acid

[0291]

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30 COOH

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TLC: Rf 0.23 (CHCl₃: MeOH = 20:1);

NMR : δ 8.16 (2H, d, J=8.4Hz), 7.56 (2H, d, J=8.4Hz), 7.21 (1H, m), 6.90 (2H, m), 5.80 (1H, m), 5.17 (2H, s), 5.07 (2H, m), 4.21 (2H, d, J=6.2Hz), 2.94 (2H, m), 2.34 (3H, s), 1.81 (2H, m), 0.86 (3H, t, J=7.4Hz).

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Example 18(82)

4-[2-[N-(2-methylprop-2-enyl)-propylsulfonylamino]-5-methylphenoxymethyl]benzoic acid

[0292]

СООН 10 15

20 TLC: Rf 0.28 (CHCl₃: MeOH = 20:1);

NMR : δ 8.16 (2H, d, J=8.2Hz), 7.54 (2H, d, J=8.2Hz), 7.23 (1H, m), 6.78 (2H, m), 5.17 (2H, s), 4.75 (2H, s), 4.18 (2H, s), 2.88 (2H, m), 2.34 (3H, s), 1.79 (2H, m), 1.78 (3H, s), 0.85 (3H, t, J=7.6Hz).

Example 18(83)

4-[2-(N-isobutyl-phenylsulphonylamino)-4-chlorophenoxymethyl]benzoic acid

[0293]

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30 СООН 35 40

TLC: Rf 0.29 (CHCl₃: MeOH = 19:1); 45

NMR : δ 8.06 (2H, d, J=8.0Hz), 7.64 (2H, d, J=8.0Hz), 7.20-7.40 (7H, m), 6.78 (1H, m), 4.80 (2H, bs), 3.40 (2H, d,

J=7.0Hz), 1.61 (1H, m), 0.90 (6H, d, J=7.0Hz).

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Example 18(84)

4-[2-(N-propyl-propylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

5 **[0294]**

10 Me COOH

20 TLC: Rf 0.52 (CHCl₃: MeOH = 9:1);

NMR : δ 8.17 (2H, d, J=8.4Hz), 7.55 (2H, d, J=8.4Hz), 7.25 (1H, d, J=8.2Hz), 6.9-6.8 (2H, m), 5.17 (2H, s), 3.56 (2H, t, J=7.4Hz), 3.0-2.8 (2H, m), 2.35 (3H, s), 1.9-1.7 (2H, m), 1.6-1.4 (2H, m), 0.89 (3H, t, J=7.2Hz), 0.84 (3H, t, J=7.4Hz).

25 Example 18(85)

4-[2-(N-isobutyl-hexylsulfonylamino)-4-methylphenoxymethyl]benzoic acid

[0295]

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Me N COOH

TLC: Rf 0.49 (CHCl₃: MeOH = 9:1);

NMR: δ 8.16 (2H, d, J=8.4Hz), 7.53 (2H, d, J=8.4Hz) 7.21 (1H, d, J=2.0Hz), 7.09 (1H, dd, J=2.0, 8.4Hz), 6.87 (1H, d, J=8.4Hz), 5.16 (2H, s), 3.45 (2H, d, J=7.0Hz), 3.0-2.8 (2H, m), 2.30 (3H, s), 1.8-1.5 (3H, m), 1.3-1.0 (6H, m), 1.0-0.8 (6H, m), 0.83 (3H, t, J=7.0Hz).

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Example 18(86)

4-[2-(N-isobutyl-pentylsulfonylamino)-4-methylphenoxymethyl]benzoic acid

5 [0296]

Me O₂S

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TLC : Rf 0.38 (CHCl₃ : MeOH : AcOH= 100 : 5 : 1);

NMR : δ 8.16 (2H, d, J=8.4Hz), 7.53 (2H, d, J=8.4Hz), 7.21 (1H, d, J=2.2Hz), 7.09 (1H, dd, J=2.2, 8.6Hz), 6.87 (1H, d, J=8.6Hz), 5.16 (2H, s), 3.45 (2H, d, J=7.2Hz), 2.91 (2H, m), 2.30 (3H, s), 1.74 (2H, m), 1.60 (1H, m), 1.17 (4H, m), 0.92 (6H, m), 0.82 (3H, m).

Example 18(87)

4-[2-[N-(prop-2-enyl)-propylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid

[0297]

F₃C OOH

45

TLC: Rf 0.33 (hexane: AcOEt = 1:1);

NMR (200MHz, CDCl₃ + 1drop of CD₃OD) : δ 8.15-8.11 (2H, m), 7.54-7.44(3H, m), 7.30-7.24 (2H, m), 5.88-5.68 (1H, m), 5.20 (2H, s), 5.12-5.10 (1H, m), 5.04-5.03 (1H, m), 4.21 (2H, d, J=6.5Hz), 2.95-2.87 (2H, m), 1.8-1.7 (1H, m), 0.84 (3H, t, J=7.5 Hz).

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Example 18(88)

4-[2-[N-(2-methylprop-2-enyl)-propylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid

5 **[0298]**

10 F₃C O COOH

N
O₂S

15

20 TLC : Rf 0.41 (hexane : AcOEt = 1 : 1);

NMR : δ 8.30 (2H, d, J=8Hz), 7.71-7.67 (2H, m), 7.62-7.56 (1H, m), 7.40-7.35 (2H, m), 5.34 (2H, s), 4.89-4.85 (2H, m), 5.34 (2H, s), 4.89-4.85 (2H, m), 5.34 (2H, s), 4.89-4.85 (2H, m), 2.0-1.8 (2H, m), 1.87 (3H, s), 1.00-0.93 (3H, m).

25 Example 18(89)

4-[2-(N-propyl-2-furanylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

[0299]

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F₃C COOH

TLC: Rf 0.38 (hexane: AcOEt = 1:1);

NMR : δ 7.81 (1H, d, J=16Hz), 7.59 (2H, d, J=8Hz), 7.42-7.37 (3H, m), 7.28-7.24 (2H, m), 7.18 (1H, d, J=1.5Hz), 6.85 (1H, dd, J=3, 1Hz), 6.49 (1H, d, J=16Hz), 6.35 (1H, dd, J=3, 2Hz), 5.03 (2H, s), 3.71-3.64 (2H, m), 1.6-1.4 (2H, m), 0.88 (3H, t, J=7Hz).

EP 0 947 500 A1

Example 18(90)

 $\hbox{$4$-[2-(N-propyl-propylsulfonylamino)-5-trifluoromethylphenoxymethyl]} benzoic acid$

5 [0300]

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F₃C COOH

TLC: Rf 0.40 (CHCl₃: MeOH = 9:1);

NMR : δ 8.17 (2H, d, J=8.2Hz), 7.56 (2H, d, J=8.2Hz), 7.49 (1H, m), 7.27 (2H, m), 5.22 (2H, s), 3.58 (2H, m), 2.91 (2H, m), 1.79 (2H, m), 1.45 (2H, m), 0.89 (3H, t, J=7.4Hz), 0.85 (3H, t, J=7.6Hz).

Example 18(91)

4-[2-(N-isobutyl-propylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0301]

35 F₃C COOH

TLC: Rf 0.45 (CHCl₃: MeOH = 9:1);

NMR : δ 8.18 (2H, d, J=8.2Hz), 7.56 (2H, d, J=8.2Hz), 7.51 (1H, m), 7.28 (2H, m), 5.23 (2H, s), 3.45 (2H, d, J=7.4Hz), 2.89 (2H, m), 1.75 (2H, m), 1.58 (1H, m), 0.90 (6H, d, J=6.8Hz), 0.84 (3H, t, J=7.4Hz).

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Example 18(92)

4-[2-(N-propyl-2-furanylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

5 [0302]

10 H₃C COOH

O₂S O

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TLC: Rf 0.38 (hexane: AcOEt = 1:1);

NMR: δ 8.13 (2H, d, J=8Hz), 7.44 (2H, d, J=8Hz), 7.25 (1H, m), 7.12 (1H, d, J=8Hz), 6.83-6.73 (3H, m), 6.33-6.30 (1H, m), 5.01 (2H, s), 3.7-3.6 (2H, m), 2.33 (3H, s), 1.52 (2H, q, J=7Hz), 0.90 (3H, t, J=7Hz).

Example 18(93)

4-[2-(N-isobutyl-2-furanylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

30 [0303]

35 Me COOH
O2S

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TLC: Rf 0.41 (hexane: AcOEt = 1:1);

NMR: δ 8.13 (2H, d, J=8Hz), 7.44 (2H, d, J=8Hz), 7.25 (1H, m), 7.15 (1H, d, J=8Hz), 6.80-6.71 (3H, m), 6.31 (1H, m), 5.0 (2H, m), 3.53 (2H, d, J=7Hz), 1.75-1.60(1H, m), 0.91 (6H, t, J=7Hz).

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Example 18(94)

 $\hbox{$4$-[2-(N-isobutyl-2-furanyl sulfonylamino)-5-trifluoromethyl phenoxymethyl] cinnamic acid}$

[0304]

F₃C O COOH

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TLC: Rf 0.44 (hexane: AcOEt = 1:1);

NMR: 6 7.81 (1H, d, J=16Hz), 7.60 (2H, d, J=8Hz), 7.41-7.37 (3H, m), 7.27-7.22 (2H, m), 7.17 (1H, m), 6.83 (1H, dd, J=3.5, 1.5Hz), 6.49 (1H, d, J=16Hz), 6.35 (1H, dd, J=3.5, 1.5Hz), 5.02 (2H, s), 3.53 (2H, d, J=7.5 Hz), 1.74-1.50 (1H, m), 0.90 (6H, d, J=6.5Hz).

Example 18(95)

4-[2-(N-propyl-phenylsulfonylamino)-5-methylphenoxymethyl]cinnamic acid

[0305]

Me O COOH

45

TLC: Rf 0.33 (CHCl₃: MeOH: AcOH= 100: 5:1);

NMR: δ 7.79 (1H, d, J=16.0Hz), 7.67 (2H, m), 7.51 (2H, d, J=8.0Hz), 7.24-7.43 (3H, m), 7.17 (2H, d, J=8.0Hz), 7.15 (1H, d, J=8.0Hz), 6.78 (1H, m), 6.68 (1H, m), 6.47 (1H, d, J=16.0Hz), 4.79 (2H, brs), 3.55 (2H, m), 2.34 (3H, s), 1.47 (2H, m), 0.87 (3H, t, J=7.2Hz).

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Example 18(96)

4-[2-(N-isobutyl-phenylsulfonylamino)-5-methylphenoxymethyl]cinnamic acid

5 **[0306]**

10 Me COOH

02S

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TLC: Rf 0.37 (CHCl3: MeOH: AcOH= 100:5:1);

NMR: δ 7.79 (1H, d, J=16.0Hz), 7.63 (2H, m), 7.51 (2H, d, J=8.2Hz), 7.24-7.46 (3H, m), 7.18 (1H, d, J=7.8Hz), 7.16 (2H, d, J=8.2Hz), 6.78 (1H, m), 6.66 (1H, m), 6.48 (1H, d, J=16.0Hz), 4.74 (2H, m), 3.41 (2H, m), 2.33 (3H, s), 1.61 (1H, m), 0.89 (6H, d, J=6.4Hz).

Example 18(97)

4-[2-(N-isobutyl-propylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

[0307]

F₃C COOH

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TLC: Rf 0.36 (CHCl3: MeOH: AcOH= 100: 5:1);

NMR : δ 7.80 (1H, d, J=16.0Hz), 7.62 (2H, d, J=8.4Hz), 7.44-7.56 (3H, m), 7.24-7.33 (2H, m), 6.50 (1H, d, J=16.0Hz), 5.17 (2H, s), 3.44 (2H, d, J=7.4Hz), 2.87 (2H, m), 7.15 (2H, m), 1.55 (1H, m), 0.90 (6H, d, J=6.6Hz), 0.83 (3H, t, J=7.4Hz).

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Example 18(98)

4-[2-(N-methyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

5 **[0308]**

F₃C O COOH

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TLC : Rf 0.44 (CHCl₃ : MeOH = 9:1);

NMR: δ 7.79 (1H, d, J=16.2Hz), 7.7-7.6 (2H, m), 7.6-7.2 (7H, m), 7.2-7.1 (3H, m), 6.49 (1H, d, J=16.2Hz), 4.88 (2H, s), 3.23 (3H, s).

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Example 18(99)

4-[2-(N-propyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

30 **[0309**]

F₃C COOH

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TLC: Rf 0.43 (CHCl₃: MeOH = 9:1);

NMR: δ 7.80 (1H, d, J=16.0Hz), 7.7-7.6 (2H, m), 7.6-7.1 (10H, m), 6.49 (1H, d, J=16.0Hz), 4.86 (2H, s), 3.57 (2H, t, J=7.2Hz), 1.6-1.3 (2H, m), 0.87 (3H, t, J=7.2Hz).

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Example 18(100)

4-[2-(N-isobutyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

[0310]

15 F₃C COOH

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TLC: Rf 0.47 (CHCl₃: MeOH = 9:1);

NMR: δ 7.80 (1H, d, J=16.0Hz), 7.7-7.1 (12H, m), 6.49 (1H, d, J=16.0Hz), 4.9-4.7 (2H, br), 3.42 (2H, d, J=7.6Hz),

1.7-1.5 (1H, m), 0.89 (6H, d, J=6.6Hz).

Example 18(101)

4-[2-(N-isopropyl-propylsulfonylamino)-5-methylphenoxymethyl]cinnamic acid

[0311]

Me COOH
O₂S

45

TLC: Rf 0.44 (CHCl₃: MeOH = 9:1);

NMR : δ 7.79 (1H, d, J=16.0Hz), 7.53 (4H, m), 7.14 (1H, m), 6.80 (2H, m), 6.47 (1H, d, J=16.0Hz), 5.07 (2H, s), 4.31 (1H, m), 2.94 (2H, m), 1.79 (2H, m), 1.23 (3H, d, J=6.6Hz), 1.08 (3H, d, J=6.6Hz), 0.83 (3H, t, J=7.2Hz).

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Example 18(102)

 $\hbox{\bf 4-[2-(N-ethyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]} cinnamic\ acid$

[0312]

TLC : Rf 0.37 (CHCl $_3$: MeOH = 9 : 1); NMR : δ 7.79 (1H, d, J=16.0Hz), 7.60-7.71 (2H, m), 7.15-7.55 (10H, m), 6.49 (1H, d, J=16.0Hz), 4.89 (2H, s), 3.67 (2H, q, J=7.0Hz), 1.09 (3H, t, J=7.0Hz).

Example 18(103)

 $\hbox{$4$-[2-(N-cyclopropylmethyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl] cinnamic acid}$

[0313]

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F₃C COOH

TLC : Rf 0.47 (CHCl₃ : MeOH = 9 : 1);

NMR: 8 7.80 (1H, d, J=16.0Hz), 7.14-7.55 (10H, m), 7.67 (2H, m), 6.49 (1H, d, J=16.0Hz), 4.88 (2H, s), 3.49 (2H, d, J=7.0Hz), 0.87 (1H, m), 0.37 (2H, m), 0.06 (2H, m).

Example 18(104)

4-[2-(N-isopropyl-methylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

5 [0314]

10 F₃C COOH

20 TLC: Rf 0.47 (CHCl₃: MeOH = 9:1);

NMR: δ 7.76 (1H, d, J=16.0Hz), 7.61 (2H, d, J=8.4Hz), 7.49 (2H, d, J=8.4Hz), 7.37 (3H, m), 6.48 (1H, d, J=16.0Hz), 5.14 (2H, s), 4.31 (1H, m), 2.89 (3H, s), 1.28 (3H, d, J=6.6Hz), 1.09 (3H, d, J=6.6Hz).

Example 18(105)

4-[2-(N-benzyl-propylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

[0315]

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35 F₃C COOH

TLC : Rf 0.29 (CHCl₃ : MeOH : AcOH = 100 : 5 : 1);

NMR: δ 7.82 (1H, d, J=16.2Hz), 7.65 (2H, d, J=8.4Hz), 7.51 (2H, d, J=8.4Hz), 7.09-7.31 (8H, m), 6.52 (1H, d,

J=16.2Hz), 5.17 (2H, s), 4.78 (2H, s), 2.94 (2H, m), 1.80 (2H, m), 0.85 (2H, t, J=7.4Hz).

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Example 18(106)

4-[2-(N-propyl-phenylsulfonylamino)-4-methylphenoxymethyl]cinnamic acid

⁵ [0316]

10 Me NO2S

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TLC: Rf 0.39 (CHCl₃: MeOH = 9:1);

NMR: δ 7.79 (1H, d, J=16.0Hz), 7.70-7.65 (2H, m), 7.50 (2H, d, J=8.0Hz), 7.42-7.38 (1H, m), 7.30 (2H, t, J=8.0Hz), 7.16 (2H, d, J=8.0Hz), 7.11 (1H, d, J=1.5Hz), 7.07 (1H, dd, J=1.5, 8.0Hz), 6.74 (1H, d, J=8.0Hz), 6.47 (1H, d, J=16.0Hz), 4.90-4.70 (2H, br), 3.70-3.50 (2H, br), 2.29 (3H, s), 1.55-1.45 (2H, m), 0.88 (3H, t, J=7.0Hz).

Example 18(107)

4-[2-[N-(prop-2-enyl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]cinnamic acid

[0317]

F₃C O COOH

45

TLC: Rf 0.35 (CHCl₃: MeOH = 9: 1);

NMR : δ 7.80 (1H, d, J=16.0Hz), 7.71-7.68 (2H, m), 7.54 (2H, d, J=8.0Hz), 7.49-7.45 (1H, m), 7.40 (1H, d, J=8.0Hz), 7.38-7.33 (2H, m), 7.25 (1H, dd, J=2.0, 8.0Hz), 7.19 (2H, d, J=8.0Hz), 7.12 (1H, d, J=2.0Hz), 6.49 (1H, d, J=16.0Hz), 5.80-5.70 (1H, m), 5.07-5.02 (2H, m), 4.88 (2H, s), 4.5-4.3 (2H, m).

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Example 18(108)

4-[2-[N-(2-methylprop-2-enyl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]cinnamic acid

5 **[0318]**

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F₃C COOH

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TLC: Rf 0.39 (CHCl₃: MeOH = 9:1);

NMR : δ 7.80 (1H, d, J=16.0Hz), 7.68-7.63 (2H, m), 7.54 (2H, d, J=8.0Hz), 7.48-7.44 (1H, m), 7.41 (1H, d, J=8.0Hz), 7.35 (2H, t, J=8.0Hz), 7.25 (1H, dd, J=1.5, 8.0Hz), 7.17 (2H, d, J=8.0Hz), 7.10 (1H, d, J=1.5Hz), 6.50 (1H, d, J=16.0Hz), 4.84 (2H, s), 4.73 (1H, s), 4.68 (1H, s), 4.20 (2H, s), 1.74 (3H, s).

Example 18(109)

4-[2-[N-(prop-2-enyl)-2-furanylsulfonylamino]-5-methylphenoxymethyl]benzoic acid

[0319]

Me COOH

45

TLC: Rf 0.21 (hexane: AcOEt = 1:1);

NMR : δ 8.14-8.13 (2H, m), 7.45 (2H, d, J=8.5Hz), 7.28 (1H, m), 7.10 (1H, d, J=7.5Hz), 6.85 (1H, m), 6.84-6.76 (1H, m), 6.71 (1H, s), 6.34 (1H, m), 5.88-5.79 (1H, m), 5.11-5.02 (4H, m), 4.33 (2H, bs), 2.32 (3H, bs).

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Example 18(110)

4-[2-[N-(2-methylprop-2-enyl)-2-furanylsulfonylamino]-5-methylphenoxymethyl]benzoic acid

5 **[0320]**

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TLC: Rf 0.24 (hexane: AcOEt = 1:1);

NMR: \$ 8.14-8.13 (2H, m), 7.44 (2H, d, J=8Hz), 7.26 (1H, m), 7.13 (1H, d, J=8Hz), 6.82 (1H, m), 6.78-6.69 (1H, m), 6.69 (1H, s), 6.33 (1H, m), 5.00 (2H, s), 4.76 (1H, dd, J=9.5, 1.5 Hz), 4.30 (2H, bs), 2.32 (3H, s), 1.78 (3H, s).

25 Example 18(111)

4-[2-(N-isobutyl-phenylsulfonylamino)-4-methylphenoxymethyl]cinnamic acid

[0321]

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Me No S

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TLC: Rf 0.37 (CHCl₃: MeOH = 9:1);

NMR: \$7.79 (1H, d, J=16.0Hz), 7.70-7.60 (2H, m), 7.50 (2H, d, J=8.0Hz), 7.40-7.35 (1H, m), 7.30-7.20 (2H, m), 7.20-7.10 (3H, m), 7.05 (1H, dd, J=2.0, 8.0Hz), 6.72 (1H, d, J=8.0Hz), 6.47 (1H, d, J=16.0Hz), 4.9-4.5 (2H, m), 3.5-3.3 (2H, m), 2.29 (3H, s), 1.7-1.6 (1H, m), 1.0-0.8 (6H, m).

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Example 18(112)

4-[2-(N-benzyl-methylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

[0322]

10 F₃C COOH

TLC : Rf 0.62 (CHCl₃ : MeOH = 9 : 1); NMR : δ 7.80 (1H, d, J=16.0Hz), 7.64 (2H, d, J=8.4Hz), 7.48 (2H, d, J=8.4Hz), 7.24 (8H, m), 6.50 (1H, d, J=16.0Hz), 5.18 (2H, s), 4.77 (2H, s), 2.88 (3H, s).

Example 18(113)

4-[2-(N-isobutyl-2-furanylsulfonylamino)-4-methylphenoxymethyl]benzoic acid

[0323]

TLC: Rf 0.26 (AcOEt: hexane = 1:1);

NMR: δ 8.11 (2H, d, J=8Hz), 7.41 (2H, d, J=8Hz), 7.25 (1H, m), 7.09 (1H, d, J=2Hz), 7.06 (1H, dt, J=8,2Hz), 6.80 (1H, dd, J=4, 1Hz), 6.76 (1H, d, J=8Hz), 6.31 (1H, dd, J=2, 2Hz), 5.20-4.80 (2H, brs), 3.53 (2H, brs), 2.28 (3H, s), 1.67 (1H, m), 0.92 (6H, brs).

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Example 18(114)

 $\hbox{$4$-[2-(N-isopropyl-2-furanyl sulfonylamino)-4-methyl phenoxymethyl]} benzoic acid$

5 [0324]

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Me O₂S O

20 TLC : Rf 0.19 (AcOEt : hexane = 1 : 1);

NMR: δ 8.12 (2H, d, J=8Hz), 7.55 (2H, d, J=8Hz), 7.44 (1H, d, J=2Hz), 7.11 (1H, dd, J=8, 2Hz), 6.91 (1H, dd, J=3, 1Hz), 6.87 (1H, d, J=3Hz), 6.84 (1H, d, J=8Hz), 6.42 (1H, dd, J=3, 1Hz), 5.10 (2H, s), 4.48 (1H, m), 2.27 (3H, s), 1.12 (6H, d, J=7Hz).

Example 18(115)

4-[2-[N-(2-methylprop-2-enyl)-2-furanylsulfonylamino]-4-methylphenoxymethyl]benzoic acid

30 [0325]

Me No Solve Cooh

TLC: Rf 0.21 (AcOEt: hexane = 1:1);

NMR : δ 8.12 (2H, d, J=8Hz), 7.42 (2H, d, J=8Hz), 7.26 (1H, m), 7.07 (1H, d, J=2Hz), 7.06 (1H, dd, J=8, 2Hz), 6.83 (1H, d, J=3Hz), 6.75 (1H, d, J=8Hz), 6.33 (1H, dd, J=3, 2Hz), 4.97 (2H, s), 4.77 (2H, s), 4.30 (2H, s), 2.28 (3H, s), 1.79 (3H, s).

Example 18(116)

4-[2-(N-isopropyl-2-furanylsulfonylamino)-5-methylphenoxymethyl]cinnamic acid

5 **[0326]**

10 Me COOH

O2S

O2S

20

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TLC: Rf 0.20 (hexane: AcOEt = 1:1);

NMR: δ 7.80 (1H, d, J=16Hz), 7.61-7.45 (4H,m), 7.43 (1H, m), 6.93-6.88 (2H, m), 6.79-6.73 (2H, m), 6.47 (1H, d, J=16Hz), 6.41 (1H, dd, J=3.5, 2Hz), 5.07 (2H, s), 4.56-4.43 (1H, m), 2.34 (3H, s), 1.10 (6H, dd, J=6.5, 4Hz).

Example 18(117)

4-[2-(N-isopropyl-2-furanylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

30 [0327]

F₃C COOH

45

TLC: Rf 0.18 (hexane: AcOEt = 1:1);

NMR: δ 7.80 (1H, d, J=16Hz), 7.63-7.51 (4H, m), 7.46 (1H, dd, J=1.5, 1Hz), 7.23-7.20 (3H, m), 6.94 (1H, dd, J=3.5, 1Hz), 6.52-6.43 (3H, m), 5.14 (2H, s), 4.51-4.41 (1H, m), 1.09 (6H, dd, J=6.5, 1Hz).

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Example 18(118)

 $\hbox{$4$-[2-(N-isopropyl-2-furanyl sulfonylamino)-4-trifluoromethyl phenoxymethyl]} benzoic acid$

5 [0328]

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F₃C N COOH

TLC: Rf 0.35 (AcOEt: hexane: AcOH= 50: 50: 1);

NMR : δ 8.16 (2H, d, J=8.5Hz), 7.60 (3H, m), 7.38 (1H, dd, J=1.0, 2.0Hz), 7.26 (1H, m), 7.05 (1H, d, J=9.0Hz), 6.95 (1H, d, J=3.0Hz), 6.47 (1H, dd, J=2.0, 3.5Hz), 5.22 (2H, s), 4.52 (1H, sept, J=7.0Hz), 1.12 (3H, d, J=7.0Hz), 1.10 (3H, d, J=7.0Hz).

Example 18(119)

4-[2-(N-isobutyl-2-furanylsulfonylamino)-4-trifluoromethylphenoxymethyl]benzoic acid

30 **[0329]**

F₃C N COOH

45

TLC : Rf 0.35 (AcOEt : hexane : AcOH= 50 : 50 : 1); NMR : δ 8.15 (2H, d, J=9.0Hz), 7.55 (1H, m), 7.48 (2H, d, J=9.0Hz), 7.44 (1H, d, J=2.0Hz), 7.35 (1H, dd, J=1.0, 2.0Hz), 6.99 (1H, d, J=9.0Hz), 6.86 (1H, dd, J=1.0, 2.0Hz), 6.39 (1H, dd, J=2.0, 4.0Hz), 5.12 (2H, br), 3.52 (2H, d, J=7.0Hz), 1.64 (1H, m), 0.92 (6H, d, J=6.5Hz).

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Example 18(120)

4-[2-(N-isopropyl-phenylsulfonylamino)-4-trifluoromethylphenoxymethyl]cinnamic acid

5 **[0330]**

10 F₃C N O₂S

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TLC: Rf 0.35 (AcOEt: hexane: AcOH= 50: 50: 1);

NMR : δ 7.81 (3H, m), 7.58-7.62 (3H, m), 7.53 (1H, m), 7.49 (2H, d, J=8.0Hz), 7.41 (2H, m), 7.24 (1H, d,J=2.0Hz), 7.07 (1H, d, J=8.5Hz), 6.49 (1H, d, J=16.5Hz), 5.13 (1H, d, J=12.5Hz), 5.12 (1H, d, J=12.5Hz), 4.40 (1H, sept, J=6.5Hz), 4.07 (3H, d, J=6.5Hz), 1.02 (3H, d, J=6.5Hz).

Example 18(121)

30 4-[2-(N-isobutyl-2-furanylsulfonylamino)-5-chlorophenoxymethyl]benzoic acid

[0331]

35 CI COOH O₂S

45

TLC: Rf 0.36 (AcOEt: hexane: AcOH= 50: 50: 1);

NMR : δ 8.14 (2H, d, J=8.5Hz), 7.44 (2H, d, J=8.5Hz), 7.26 (1H, m), 7.21 (1H, d, J=9.0Hz), 6.98 (1H, dd, J=2.5, 8.0Hz), 6.91 (1H, d, J=2.5Hz), 6.82 (1H, d, J=4.5Hz), 6.34 (1H, d, J=2.0, 3.0Hz), 5.00 (2H, br), 3.51 (2H, brs), 1.65 (1H, m), 0.91 (6H, d, J=6.5Hz).

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Example 18(122)

4-[2-(N-isopropyl-2-furanylsulfonylamino)-5-chlorophenoxymethyl]cinnamic acid

5 **[0332]**

10 CI COOH

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TLC: Rf 0.49 (CHCl₃: MeOH = 9:1);

NMR : δ 7.80 (1H, d, J=16.2Hz), 7.60 (2H, d, J=8.4Hz), 7.50 (2H, d, J=8.4Hz), 7.45-7.42 (1H, m), 7.02-6.90 (4H, m), 6.53-6.40 (2H, m), 5.07 (2H, s), 4.60-4.40 (1H, m), 1.10 (3H, d, J=6.6Hz), 1.07 (3H, d, J=6.6Hz).

Example 18(123)

4-[2-(N-isobutyl-2-furanylsulfonylamino)-5-chlorophenoxymethyl]cinnamic acid

30 [0333]

CI COOH

45

TLC: Rf 0.49 (CHCl₃: MeOH = 9:1);

NMR : δ 7.80 (1H, d, J=15.8Hz), 7.58 (2H, d, J=8.0Hz), 7.37 (2H, d, J=8.0Hz), 7.25 (1H, dd, J=1.0, 1.8Hz), 7.20 (1H, d, J=8.2Hz), 7.00-6.90 (2H, m), 6.81 (1H, dd, J=1.0, 3.6Hz), 6.49 (1H, d, J=15.8Hz), 6.33 (1H, dd, J=1.8, 3.6Hz), 4.95 (2H, s), 3.60-3.40 (2H, m), 1.80-1.50 (1H, m), 0.90 (6H, d, J=6.6Hz).

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Example 18(124)

4-[2-(N-isobutyl-2-furanylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

5 [0334]

F₃C COOH

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TLC: Rf 0.20 (hexane: AcOEt = 1:1);

NMR: δ 8.18-8.14 (2H, m), 7.48-7.40 (2H, m), 7.30-7.26 (2H, m), 7.16 (1H, m), 6.84 (1H, dd, J=3.5,1 Hz), 6.35 (1H, dd, J=3.5, 2Hz), 5.07 (2H, s), 3.54 (2H, d, J=7Hz), 1.64 (1H, sept., J=7Hz), 0.90 (6H, d, J=7Hz).

Example 18(125)

4-[2-(N-isobutyl-2-furanylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid

30 **[0335]**

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CI NO2S O

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TLC: Rf 0.36 (CHCl₃: MeOH = 9:1);

NMR : δ 8.14 (2H, d, J=8.4Hz), 7.44 (2H, d, J=8.4Hz), 7.34-7.20 (3H, m), 6.90-6.80 (2H, m), 6.37 (1H, dd, J=1.8, 3.0Hz), 5.03 (2H, s), 3.51 (2H, d, J=7.2Hz), 1.80-1.50 (1H, m), 0.91 (6H, d, J=6.6Hz).

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Example 18(126)

4-[2-(N-isobutyl-2-furanylsulfonylamino)-4-methylphenoxymethyl]cinnamic acid

5 [0336]

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Me O₂S O

TLC : Rf 0.33 (CHCl₃ : MeOH = 9 : 1);

NMR : δ 7.80 (1H, d, J=16.0Hz), 7.57 (2H, d, J=8.0Hz), 7.36 (2H, d, J=8.0Hz), 7.28-7.22 (1H, m), 7.12-7.02 (2H, m), 6.84-6.74 (2H, m), 6.48 (1H, d, J=16.0Hz), 6.32 (1H, ddt J=1.8, 3.6Hz), 4.92 (2H, s), 3.54 (2H, d, J=7.0Hz), 2.28 (3H, s), 1.80-1.60 (1H, m), 0.92 (6H, d, J=6.6Hz).

Example 18(127)

4-[2-(N-isobutyl-4-ethoxyphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

30 [0337]

F₃C COOH
O₂S
O₂S
O₂S

TLC: Rf 0.35 (CHCl₃: MeOH: AcOH= 100:5:1);

NMR : δ 8.09 (2H, d, J=8.5Hz), 7.52 (2H, d, J=8.5Hz), 7.46 (1H, d, J=8.5Hz), 7.25-7.29 (3H, m), 7.13 (1H, brd, J=1.5Hz), 6.73 (2H, d, J=9.0Hz), 4.92 (2H, br), 3.96 (2H, q, J=7.5Hz), 3.40 (2H, brs), 1.59 (1H, m), 1.42 (3H, t, J=7.5Hz), 0.90 (6H, brd, J=6.0Hz).

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Example 18(128)

4-[2-(N-methyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid

[0338]

10 CI N COOH

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TLC: Rf 0.43 (CHCl₃: MeOH: H₂O = 9:1:0.1);

NMR (DMSO-d₆): δ 7.88 (2H, d, J=8.6Hz), 7.66-7.38 (6H, m), 7.25-7.11 (4H, m), 4.95 (2H, s), 3.15 (3H, s).

25 Example 19

[0339]

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[0340] To a solution of methyl 4-(2-phenylsulfonylamino-5-trifluoromethylphenoxymethyl)benzoate (251 mg; prepared in Example 15.), triphenylphosphine (142 mg) and cyclopentylmethanol (54 mg) in THF (2 ml), diethyl azodicarboxylate (89 ml; abbreviated as DEAD.) was added at 0°C. The mixture was stirred overnight at room temperature. The reaction solution was purified on silica gel chromatography (hexane: AcOEt = 7:1) to give the title compound (333 mg) having the following physical data.

TLC: Rf 0.51 (hexane: AcOEt = 3:1);

NMR: 8 8.01 (2H, d, J=8.4Hz), 7.63-7.58 (2H, m), 7.48-7.25 (5H, m), 7.17 (2H, d, J=8.4Hz), 7.09 (1H, d, J=1.4Hz), 4.83 (2H, br), 3.95 (3H, s), 3.55 (2H, d-like), 1.92-1.09 (9H, m).

Example 20

4-[2-(N-cyclopentylmethyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl)benzoic acid

5 [0341]

F₃C O COOH

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[0342] By using methyl 4-[2-(N-cyclopentylmethyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoate (prepared in Example 19.), the title compounds having the following physical data was obtained by the same procedure as Example 2.

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TLC : Rf 0.40 (CHCl₃ : MeOH : $H_2O = 9 : 1 : 0.1$); NMR : δ 8.09 (2H, d, J=8.2Hz), 7.65-7.61 (2H, m), 7.47-7.20 (7H, m), 7.11 (1H, d, J=1.8Hz), 4.89 (2H, br), 3.59-3.51 (2H, m), 1.93-1.10 (9H, m).

30 Example 20(1)-20(30)

[0343] By using the corresponding compounds, the title compounds having the following physical data were obtained by the same procedure as Reference Example 6—Reference Example 7—Example 7—Example 19—Example 2 or Reference Example 8—Reference Example 9—Reference Example 10—Example 19—Example 2.

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Example 20(1)

4-[2-(N-cyclopropylmethyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

40 [0344]

F₃C O COOH

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TLC : Rf 0.43 (CHCl₃ : MeOH : $H_2O = 9 : 1 : 0.1$); NMR : δ 8.09 (2H, d, J=8.2Hz), 7.70-7.65 (2H, m), 7.54-7.22 (7H, m), 7.14 (1H, d, J=1.8Hz), 4.93 (2H, s), 3.51 (2H, m), 7.54-7.22 (7H, m), 7.14 (1H, d, J=1.8Hz), 4.93 (2H, s), 3.51 (2H, m), 7.54-7.22 (7H, m), 7.14 (1H, d, J=1.8Hz), 4.93 (2H, s), 3.51 (2H, m), 7.54-7.22 (7H, m), 7.14 (1H, d, J=1.8Hz), 4.93 (2H, s), 3.51 (2H, m), 7.54-7.22 (7H, m), 7.14 (1H, d, J=1.8Hz), 4.93 (2H, s), 3.51 (2H, m), 7.54-7.22 (7H, m), 7.54-7.22 (

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d, J=7.2Hz), 0.96-0.81 (1H, m), 0.44-0.35 (2H, m), 0.10-0.02 (2H, m).

Example 20(2)

4-[2-(N-t-butylmethyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0345]

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СООН

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TLC: Rf 0.5 (CHCl₃: MeOH = 9:1);

NMR: δ 8.12 (2H, d, J=8.0Hz), 7.6-7.4 (4H, m), 7.4-7.2 (5H, m), 7.09 (1H, d, J=1.8Hz), 5.02 (1H, d, J=12.4Hz),

4.72 (1H, d, J=12.4Hz), 3.53 (2H, s), 0.86 (9H, s).

Example 20(3)

4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]phenylacetic acid

[0346]

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СООН

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TLC: Rf 0.47 (CHCl3: MeOH: AcOH= 100:5:1); 50

NMR: δ 7.79 (2H, d, J=7.6Hz), 7.20-7.50 (10H, m), 5.01 (2H, s), 4.28 (1H, sept, J=6.6Hz), 3.71 (2H, s), 1.08 (3H,

d, J=6.6Hz), 1.01 (3H, d, J=6.6Hz).

Example 20(4)

 $\hbox{\bf 4-[2-(N-isopropyl-propylsulfonylamino)-5-trifluoromethylphenoxymethyl]} benzoic\ acid$

[0347]

COOH 10 15

TLC: Rf 0.33 (CHCl3: MeOH = 20:1); 20

NMR (CD₃Cl): δ 8.13 (2H, d, J=8.0Hz), 7.54 (2H, d, J=8.0Hz), 7.30-7.46 (3H, m), 5.19 (2H, s), 4.32 (1H, sept, J=6.2Hz), 2.96 (2H, m), 1.78 (2H, m), 1.27 (2H, d, J=6.4Hz), 1.12 (2H, d, J=6.4Hz), 0.85 (3H, t, J=7.4Hz).

Example 20(5)

4-[2-(N-isopropyl-pentylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0348]

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COOH

TLC: Rf 0.40 (CHCl₃: MeOH = 20:1);

NMR (CD₃Cl) : δ 8.17 (2H, d, J=8.4Hz), 7.59 (2H, d, J=8.4Hz), 7.12-7.41 (3H, m), 5.18 (2H, s), 4.32 (1H, sept,

J=6.6Hz), 2.97 (2H, m), 1.74 (2H, m), 1.02-1.35 (8H, m), 0.82 (3H, t, J=6.8Hz).

Exampl 20(6)

4-[2-(N-isopropyl-butylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

5 **[0349**]

F₃C COOH

TLC: Rf 0.40 (CHCl₃: MeOH = 9:1);

NMR : δ 8.17 (2H, d, J=8.2Hz), 7.59 (2H, d, J=8.2Hz), 7.40 (1H, d, J=7.8Hz), 7.3-7.2 (2H, m), 5.18 (2H, s), 4.4-4.2 (1H, m), 3.1-2.9 (2H, m), 1.8-1.6 (2H, m), 1.4-1.0 (8H, m), 0.92 (3H, t, J=7.2Hz).

25 Example 20(7)

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4-[2-(N-isopropyl-hexylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0350]

F₃C COOH

TLC: Rf 0.44 (CHCl3: MeOH = 9:1);

NMR: δ 8.18 (2H, d, J=8.0Hz), 7.59 (2H, d, J=8.0Hz), 7.40 (1H, d, J=8.0Hz), 7.3-7.2 (2H, m), 5.18 (2H, s), 4.4-4.2 (1H, m), 3.0-2.9 (2H, m), 1.8-1.6 (2H, m), 1.3-1.0 (12H, m), 0.85 (3H, t, J=7.4Hz).

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Example 20(8)

4-[2-(N-isopropyl-heptylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0351]

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20 TLC : Rf 0.48 (CHCl₃ : MeOH = 9 : 1);

NMR: 88.18 (2H, d, J=8.0Hz), 7.59 (2H, d, J=8.0Hz), 7.40 (1H, d, J=8.0Hz), 7.3-7.2 (2H, m), 5.18 (2H, s), 4.4-4.2 (1H, m), 3.0-2.9 (2H, m), 1.9-1.6 (2H, m), 1.4-1.0 (14H, m), 0.86 (3H, t, J=6.2Hz).

25 **Example 20(9)**

4-[2-(N-isopropyl-4-hydroxyphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0352]

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COOH 025

TLC: Rf 0.28 (CHCl₃: MeOH = 9:1);

NMR: δ 8.13 (2H, d, J=8.2Hz), 7.66 (2H, d, J=9.2Hz), 7.50 (2H, d, J=8.2Hz), 7.3-7.2 (3H, m), 6.72 (2H, d, J=9.2Hz), 5.10 (2H, s), 4.4-4.2 (1H, m), 3.0-1.5 (2H, br), 1.10 (3H, d, J=6.6Hz), 1.03 (3H, d, J=6.6Hz).

Example 20(10)

4-[2-(N-isopropyl-butylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

5 **[0353]**

10 Me COOH

NO 25

20 TLC : Rf 0.41 (CHCl₃ : MeOH = 9 : 1); NMP : 8.9.15 (2H d. L-9.5Hz) 7.57 (2H d. L-9.5Hz)

NMR: δ 8.15 (2H, d, J=8.6Hz), 7.57 (2H, d, J=8.6Hz), 7.15 (1H, d, J=8.4Hz), 6.9-6.8 (2H, m), 5.13 (2H, s), 4.4-4.2 (1H, m), 3.1-2.9 (2H, m), 2.36 (3H, s), 1.8-1.6 (2H, m), 1.3-1.2 (5H, m), 1.10 (3H, d, J=6.6Hz), 0.81 (3H, t, J=7.4Hz).

Example 20(11)

4-[2-(N-isopropyl-hexylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

[0354]

30 COOH

Me

O

S

O

S

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TLC: Rf 0.47 (CHCl₃: MeOH = 9:1);

NMR: 88.15 (2H, d, J=8.4Hz), 7.57 (2H, d, J=8.4Hz), 7.15 (1H, d, J=8.4Hz), 7.1-7.0 (2H, m), 5.13 (2H, s), 4.4-4.2 (1H, m), 3.0-2.9 (2H, m) 2.36 (3H, s), 1.8-1.6 (2H, m), 1.3-1.0 (12H, m), 0.84 (3H, t, J=6.4Hz).

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Example 20(12)

4-[2-(N-isopropyl-heptylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

5 **[0355**]

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Me O COOH

TLC : Rf 0.47 (CHCl₃ : MeOH = 9 : 1);

NMR : δ 8.15 (2H, d, J=8.0Hz), 7.57 (2H, d, J=8.0Hz), 7.15 (1H, d, J=8.4Hz), 6.9-6.8 (2H, m), 5.13 (2H, s), 4.4-4.2 (1H, m), 3.0-2.9 (2H, m), 2.36 (3H, s), 1.9-1.6 (2H, m), 1.3-1.0 (14H, m), 0.85 (3H, t, J=6.2Hz).

Example 20(13)

4-[2-(N-isopropyl-methylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

[0356]

Me COOH

TLC: Rf 0.13 (hexane: AcOEt = 1:1);

NMR : δ 8.17-8.13 (2H, m), 7.58-7.53 (2H, m), 7.17-7.12 (1H, m), 6.8 (2H, m), 5.1 (2H, m), 4.33 (1H, sept., J=6.5Hz), 2.90 (3H, s), 2.36 (3H, s), 1.26 (3H, d, J=6.5Hz), 1.09 (3H, d, J=6.5Hz).

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Example 20(14)

4-[2-(N-isopropyl-ethylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

[0357]

10 Me COOH

O2S

20 TLC: Rf 0.20 (hexane: AcOEt = 1:1);

NMR : δ 8.17-8.13 (2H, m), 7.59-7.55 (2H, m), 7.17-7.13 (1H, m), 6.8 (2H, m), 5.1 (2H, m), 4.33 (1H, sept., J=7Hz), 3.01 (2H, q, J=7Hz), 2.36 (3H, s), 1.29-1.20 (6H, m), 1.09 (3H, d, J=6.5Hz).

Example 20(15)

4-[2-(N-isopropyl-2-phenylethylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

[0358]

35 Me COOH
O2S

45 TLC: Rf 0.24 (hexane: AcOEt = 1:1);

NMR: δ 8.00-7.96 (2H, m), 7.44-7.40 (2H, m), 7.26-7.14 (4H, m), 7.05-7.01 (2H, m), δ 6.85-6.81 (2H, m), 5.07 (2H, s), 4.42-4.27 (1H, m), 3.4-3.2 (2H, m), 3.2-3.0 (2H, m), 2.36 (3H, s), 1.25 (3H, d, J= δ 5.5Hz), 1.09 (3H, d, J= δ 5.5Hz).

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Example 20(16)

4-[2-(N-isopropyl-benzylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

⁵ [0359]

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Me COOH

TLC: Rf 0.22 (hexane: AcOEt = 1:1);

NMR : δ 8.15-8.11 (2H, m), 7.63-7.59 (2H, m), 7.3 (2H, m), 6.92-6.88 (1H, m), 6.81-6.70 (2H, m), 5.2 (2H, m), 4.29 (2H, s), 4.18-4.02 (1H, m), 2.35 (3H, s), 1.12 (3H, d, J=6.5Hz), 1.04 (3H, d, J=6.5Hz).

Example 20(17)

4-[2-(N-t-butylmethyl-phenylsulfonylamino)-4-methylphenoxymethyl]benzoic acid

[0360]

Me NO2S

45 TLC: Rf 0.37 (CHCl₃: MeOH = 9:1);

NMR : δ 8.08 (2H, d, J=8Hz), 7.55 (2H, m), 7.39 (1H, m), 7.32-7.20 (4H, m), 7.17 (1H, d, J=2Hz), 7.03 (1H, dd, J=8 and 2Hz), 6.68 (1H, d, J=8Hz), 4.90 (1H, d, J=13Hz), 4.59 (1H, d, J=13Hz), 3.57 (1H, d, J=14Hz), 3.50 (1H, d, J=14Hz), 2.28 (3H, s), 0.88 (9H, s).

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Example 20(18)

4-[2-(N-isopropyl-methylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

5 **[0361]**

F₃C COOH
O₂S

20 TLC: Rf 0.32 (CHCl₃: MeOH = 9:1);

NMR: δ 8.17 (2H, d, J=8.5Hz), 7.58 (2H, d, J=8.5Hz), , 7.43-7.23 (3H, m), 5.20 (2H, s), 4.32 (1H, m), 2.91 (3H, s), 1.29 (3H, d, J=7Hz), 1.10 (3H, d, J=7Hz).

Example 20(19)

4-[2-(N-isopropyl-ethylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0362]

35 F₃C COOH

TLC: Rf 0.36 (CHCl₃: MeOH = 9:1);

NMR : δ 8.18 (2H, d, J=8.5Hz), 7.59 (2H, d, J=8.5Hz), , 7.43-7.23 (3H, m), 5.19 (2H, s), 4.33 (1H, m), 3.03 (2H, q, J=7.5Hz), 1.32-1.17 (6H, m), 1.09 (3H, d, J=7Hz).

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Example 20(20)

 $\hbox{\bf 4-[2-(N-isopropyl-cyclopentyl methyl sulfonylamino)-5-methyl phenoxymethyl]} benzo ic\ acid$

5 [0363]

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Me COOH

TLC : Rf 0.26 (hexane : AcOEt = 1 : 1);

NMR : δ 8.17-8.13 (2H, m), 7.59-7.55 (2H, m), 7.16-7.12 (1H, m), 6.83-6.80 (2H, m), 5.13 (2H, s), 4.31 (1H, sept., J=7Hz), 3.04-3.00 (2H, m), 2.36 (3H, s), 2.4-2.2 (1H, m), 2.0-1.8 (2H, m), 1.6-1.4 (4H, m), 1.24 (3H, d, J=7Hz), 1.3-1.1 (2H, m), 1.09 (3H, d, J=7Hz).

Example 20(21)

4-[2-(N-cyclohexylmethyl-propylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

30 [0364]

Me O₂S COOH

TLC : Rf 0.43 (CHCl₃ : MeOH = 9 : 1);

NMR : δ 8.16 (2H, d, J=8.6Hz), 7.54 (2H, d, J=8.6Hz), 7.26 (1H, d, J=8.6Hz), 6.9-6.8 (2H, m), 5.17 (2H, s), 3.5-3.4 (2H, m), 2.9-2.8 (2H, m), 2.35 (3H, s), 2.0-1.0 (13H, m), 0.84 (3H, t, J=8.0Hz), 4.0-1.0 (1H, br).

Example 20(22)

4-[2-(N-cyclopentylmethyl-propylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

5 **[0365]**

10 Me COOH

TLC: Rf 0.38 (CHCl₃: MeOH = 9:1);

NMR: δ 8.16 (2H, d, J=8.4Hz), 7.54 (2H, d, J=8.4Hz), 7.26 (1H, d, J=8.4Hz), 6.9-6.8 (2H, m), 5.17 (2H, s), 3.6-3.5 (2H, m), 2.9-2.8 (2H, m), 2.35 (3H, s), 2.0-1.0 (11H, m), 0.84 (3H, t, J=7.6Hz), 6.0-4.0 (1H, br).

Example 20(23)

4-[2-(N-isopropyl-propylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

[0366]

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35 F₃C СООН

TLC : Rf 0.32 (CHCl₃ : MeOH : AcOH= 100 : 5 : 1);

NMR: δ 7.80 (1H, d, J=16.2Hz), 7.61 (2H, d, J=8.6Hz), 7.51 (2H, d, J=8.6Hz), 7.39 (1H, d, J=8.8Hz), 7.24-7.33 (2H, m), 6.49 (1H, d, J=16.2Hz), 5.12 (2H, s), 4.31 (1H, m), 2.95 (2H, m), 1.77 (2H, m), 1.26 (3H, d, J=6.6Hz), 1.09 (3H, d, J=6.6Hz), 0.82 (3H, t, J=7.2Hz).

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Example 20(24)

4-[2-(N-isopropyl-pentylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

5 **[0367]**

10 F₃C COOH

TLC: Rf 0.27 (CHCl₃: MeOH: AcOH= 100: 5:1);
NMR: δ 7.80 (1H, d, J=16.0Hz), 7.61 (2H, d, J=8.4Hz), 7.51 (2H, d, J=8.4Hz), 7.39 (1H, m), 7.24-7.33 (2H, m), 6.48 (1H, d, J=16.0Hz), 5.12 (2H, s), 4.31 (1H, sept, J=6.6Hz), 2.96 (2H, m), 1.72 (2H, m), 1.26 (3H, d, J=6.6Hz), 1.05-1.23 (7H, m), 0.83 (3H, t, J=6.2Hz).

25 <u>Example 20(25)</u>

4-[2-(N-isopropyl-2-furanylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0368]

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F₃C OOH

TLC: Rf 0.22 (hexane: AcOEt = 1:1);

NMR : δ 8.15 (2H, d,J=8Hz), 7.59 (2H, d, J=8Hz), 7.46 (1H, dd, J=2, 1Hz), 7.23 (3H, m), 6.94 (1H, dd, J=3.5, 1Hz), 6.44 (1H, dd, J=3.5, 2Hz), 5.18 (2H, s), 4.49 (1H, m), 1.10 (6H, dd, J=7, 2.5Hz).

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Example 20(26)

4-[2-(N-isopropyl-2-thienylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0369]

COOH 10 15

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TLC: Rf 0.24 (hexane: AcOEt = 1:1);

NMR: δ 8.15 (2H, d, J=8.5Hz), 7.57 (2H, d, J=8.5Hz), 7.54-7.51 (2H, m), 7.25 (3H, m), 7.01-6.99 (1H, m), 5.19 (2H, m), 7.54-7.51 (2H, m), 7.25 (3H, m), 7.01-6.99 (1H, m), 5.19 (2H, m), 7.54-7.51 (2H, m), 7.25 (3H, m), 7.01-6.99 (1H, m), 5.19 (2H, m), 7.54-7.51 (2H, m), 7.25 (3H, m), 7.01-6.99 (1H, m), 5.19 (2H, m), 7.25 (3H, m), 7.01-6.99 (1H, m), 7.

s), 4.49-4.44 (1H, m), 1.10 (6H, d, J=6.5Hz).

Example 20(27)

4-[2-(N-isopropyl-4-chlorophenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0370]

СООН 028

45

TLC: Rf 0.43 (CHCl3: MeOH = 10:1);

NMR (DMSO- d_6): δ 7.93 (2H, d, J=8.4Hz), 7.73 (2H, d, J=8.4Hz), 7.56 (1H, s), 7.50-7.28 (6H, m), 5.22 (2H, s),

4.38 (1H, sept, J=6.6Hz), 1.00 (3H, d, J=6.6Hz), 0.93 (3H, d, J=6.6Hz).

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Example 20(28)

4-[2-(N-isopropyl-4-ethylphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

5 [0371]

F₃C C₂H₅

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TLC: Rf 0.40 (CHC i_3 : MeOH = 10:1);

NMR (DMSO-d₆) : δ 7.94 (2H, d, J=8.4Hz), 7.66 (2H, d, J=8.4Hz), 7.55 (1H, d, J=1Hz), 7.49 (2H, d, J=8.4Hz), 7.39 (1H, dd, J=8.4Hz, 1Hz), 7.32 (1H, d, J=8.4Hz), 7.23 (2H, d, J=8.4Hz), 5.25 (2H, s), 4.14 (1H, sept, J=6.6Hz), 2.61 (2H, q, J=7.4Hz), 1.14 (3H, t, J=7.4Hz), 1.00 (3H, d, J=6.6Hz), 0.93 (3H, d, J=6.6Hz).

Example 20(29)

4-[2-(N-isopropyl-4-propylphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0372]

F₃C O COOH

45

TLC: Rf 0.41 (CHCl₃: MeOH = 10:1);

NMR (DMSO- d_6): δ 7.94 (2H, d, J=8.4Hz), 7.65 (2H, d, J=8.4Hz), 7.55 (1H, d, J=1Hz), 7.50 (2H, d, J=8.4Hz), 7.39 (1H, dd, J=8.4Hz, 1Hz), 7.32 (1H, d, J=8.4Hz), 7.20 (2H, d, J=8.4Hz), 5.25 (2H, s), 4.13 (1H, sept, J=6.6Hz), 2.55 (2H, t, J=7.4Hz), 1.54 (2H, tq, J=7.4Hz, 7.4Hz), 0.97 (3H, d, J=6.6Hz), 0.90 (3H, d, J=6.6Hz), 0.84 (3H, t, J=7.4Hz).

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Example 20(30)

4-[2-(N-isopropyl-4-butylphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

⁵ [0373]

F₃C COOH

20

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10

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TLC: Rf 0.41 (CHC i_3 : MeOH = 10:1);

NMR (DMSO- d_6): δ 7.94 (2H, d, J=8.4Hz), 7.65 (2H, d, J=8.4Hz), 7.55 (1H, d, J=1Hz), 7.49 (2H, d, J=8.4Hz), 7.38 (1 H, dd, J=8.4Hz), 7.33 (1H, d, J=8.4Hz), 7.20 (2H, d, J=8.4Hz), 5.24 (2H, s), 4.14 (1H, sept, J=6.6Hz), 2.57 (2H, t, J=7.4Hz), 1.49 (2H, m), 1.25 (2H, m), 0.98 (3H, d, J=6.6Hz), 0.89 (3H, d, J=6.6Hz), 0.87 (3H, t, J=7.4Hz).

Example 21-21(16)

30 [0374] By using 2-nitrophenol or the corresponding compounds, the title compounds having the following physical data were obtained by the same procedure as Reference Example 6→Reference Example 12→Reference Example 2→Example 2.

Example 21

4-(2-phenylsulfonylaminophenoxymethyl)benzoic acid

[0375]

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NH O2S

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TLC : Rf 0.35 (AcOEt : hexane : AcOH = 6 : 13 : 1); NMR (DMSO-d₆) : δ 12.86 (1H, brs), 9.53 (1H, brs), 7.91 (2H, d, J=8.0Hz), 7.66 (2H, d, J=8.0Hz), 7.52 (1H, t, J=7.0Hz), 7.45-7.25 (5H, m), 7.08 (1H, t, J=9.0Hz), 6.95-6.80 (2H, m), 4.91 (2H, s).

Example 21(1)

4-[2-(4-chlorophenylsulfonylamino)phenoxymethyl]benzoic acid

[0376]

10 NH O₂S

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TLC : Rf 0.39 (AcOEt : hexane : AcOH= 6 : 13 : 1); NMR (DMSO-d₆) : δ 12.85 (1H, brs), 9.68 (1H, brs), 7.93 (2H, d, J=8.5Hz), 7.60 (2H, d, J=8.5Hz), 7.36 (4H, d, J=8.5Hz), 7.35-7.25 (1H, m), 7.12 (1H, dt, J=7.5, 2.0Hz), 6.96-6.85 (2H, m), 4.92 (2H, s).

Example 21(2)

4-(2-phenylsulfonylamino-4-fluorophenoxymethyl)benzoic acid

[0377]

35 F NH O₂S

45

TLC : Rf 0.37 (AcOEt : hexane : AcOH= 6 : 13 : 1); NMR (DMSO-d₆) : δ 12.95 (1H, brs), 9.90 (1H, brs), 7.90 (2H, d, J=8.5Hz), 7.72 (2H, d, J=7.0Hz), 7.58 (1H, m), 7.46 (2H, t, J=7.5Hz), 7.37 (2H, d, J=8.5Hz), 7.10 (1H, d, J=9.5Hz), 6.92 (2H, d, J=7.0Hz), 4.95 (2H, s).

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Example 21(3)

4-(2-phenylsulfonylamino-5-fluorophenoxymethyl)benzoic acid

5 **[0378**]

FONH COOH

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TLC : Rf 0.42 (AcOEt : hexane : AcOH= 6 : 13 : 1); NMR (DMSO-d₆) : δ 12.95 (1H, brs), 9.65 (1H, brs), 7.91 (2H, d, J=8.5Hz), 7.60 (2H, d, J=7.0Hz), 7.52 (1H, t, J=7.0Hz), 7.39 (2H, d, J=7.5Hz), 7.35 (2H, d, J=7.5Hz), 7.26 (1H, dd, J=7.0, 6.5Hz), 6.84 (1H, dd, J=11.0, 2.5Hz), 6.75 (1H, dt, J=8.5, 2.5Hz), 4.90 (2H, s).

Example 21(4)

30 4-(2-phenylsulfonylamino-4-bromophenoxymethyl)benzoic acid

[0379]

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TLC: Rf 0.25 (AcOEt: hexane: AcOH= 6: 13: 1);
NMR (DMSO-d₆): δ 12.97 (1H, brs), 9.97 (1H, brs), 7.90 (2H, d, J=8.0Hz), 7.69 (2H, dd, J=7.5, 2Hz), 7.58 (1H, tt, J=7.5, 2Hz), 7.46 (2H, d, J=7.5Hz), 7.39 (1H, d, J=2.5Hz), 7.36 (2H, d, J=8.0Hz), 7.27 (1H, dd, J=9.0, 2.5Hz), 6.89 (1H, d. J=9Hz), 4.97 (2H, s).

EP 0 947 500 A1

Example 21(5)

4-(2-phenylsulfonylamino-5-chlorophenylthiomethyl)benzoic acid

5 [0380]

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TLC: Rf 0.50 (CHCl3: MeOH: AcOH= 100: 5:1);

NMR: 67.99 (2H, d, J=8.4Hz), 7.78 (2H, m), 7.41-7.62 (5H, m), 7.23 (1H, dd, J=2.6, 8.8Hz), 7.08 (1H, d, J=2.6Hz),

COOH

7.05 (2H, d, J=8.6Hz), 3.71 (2H, s).

Example 21(6)

4-(2-phenylsulfonylamino-4-methoxyphenoxymethyl)benzoic acid

[0381]

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TLC: Rf 0.38 (CHCl₃: MeOH = 17:3);

NMR (DMSO-d₆): δ 7.90 (2H, d, J=8.5Hz), 7.71 (2H, d, J=8.0Hz), 7.64-7.35 (5H, m), 6.90-6.80 (2H, m), 6.44 (1H,

dd, J=9.0 and 3.0Hz), 4.89 (2 H, s), 3.65 (3 H, m).

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Example 21(7)

4-(2-phenylsulfonylamino-4-trifluoromethylphenoxymethyl)benzoic acid

5 [0382]

10 F₃C NH O₂S

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TLC: Rf 0.32 (CHCl₃: MeOH = 17:3);

NMR (DMSO-d₆) : δ 7.92 (2H, d, J=8.5Hz), 7.69 (2H, d, J=8.0Hz), 7.63-7.34 (7H, m),7.11 (1H, d, J=8.5Hz), 5.09 (2H, s).

Example 21(8)

4-(2-phenylsulfonylamino-4-methylphenoxymethyl)benzoic acid

[0383]

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Me O₂S COOH

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40

TLC: Rf 0.43 (AcOEt: hexane: AcOH= 7:12:1);

NMR (DMSO- d_6): δ 7.89 (2H, d, J=8.0Hz), 7.66 (2H, d, J=7.0Hz), 7.60-7.48 (1H, m), 7.41 (2H, d, J=8.0Hz), 7.35 (2H, d, J=8Hz), 7.11 (1H, d, J=2.0Hz), 6.90 (1H, dd, J=8.0, 2.0Hz), 6.76 (1H, d, J=8Hz), 4.88 (2H, s), 2.19 (3H, s).

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Example 21(9)

4-(2-phenylsulfonylamino-5-methylphenoxymethyl)benzoic acid

[0384]

10 Me COOH
NH
O2S

20

TLC : Rf 0.43 (AcOEt : hexane : AcOH= 7 : 12 : 1); NMR (DMSO- d_6) : δ 7.91 (2H, d, J=8.5Hz), 7.62 (2H, d, J=7.0Hz), 7.57-7.45 (1H, m), 7.44-7.30 (4H, m), 7.14 (1H, d, J=8.0Hz), 6.75 (1H, s), 6.71 (1H, d, J=8.0Hz), 4.88 (2H, s), 2.21 (3H, s).

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Example 21(10)

4-(2-benzylsulfonylamino-5-chlorophenoxymethyl)benzoic acid

30 **[0385]**

CI ONH O2S

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TLC : Rf 0.52 (CHCl $_3$: MeOH : AcOH= 100 : 5 : 1); NMR (DMSO-d $_6$) : δ 7.96 (2H, d, J=8.0Hz), 7.67 (2H, d, J=8.0Hz), 7.29 (5H, s), 7.21 (1H, d, J=8.2Hz), 7.20 (1H, d, J=2.4Hz), 6.95 (1H, dd, J=2.4, 8.2Hz), 5.31 (2H, s), 4.38 (2H, s).

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Example 21(11)

4-(2-phenylsulfonylamino-5-methoxyphenoxymethyl)benzoic acid

5 **[0386]**

MeO COOH

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TLC : Rf 0.40 (CHCl₃ : MeOH = 4 : 1);

NMR (DMSO-d₆): δ 7.90 (2H, d, J=8.5Hz), 7.59 (2H, d, J=8Hz), 7.51 (1H, t, J=8Hz), 7.44-7.28 (4H, m), 7.15 (1H, d, J=8.5Hz), 6.54-6.47 (2H, m), 4.86 (2H, s), 3.69 (3H, s).

Example 21(12)

3-(2-phenylsulfonylamino-5-chlorophenoxymethyl)benzoic acid

[0387]

о СІ СООН NН О2S

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TLC: Rf 0.48 (AcOEt: hexane: AcOH= 7:12:1);

NMR (DMSO- d_6) : δ 13.03 (1H, brs), 9.80 (1H, brs), 7.98 (1H, s), 7.95-7.86 (1H, m), 7.66 (2H, d, J=7.0Hz), 7.58-7.46 (3H, m), 7.40 (2H, t, J=7.0Hz), 7.27 (1H, d, J=8.5Hz), 7.07 (1H, d, J=2.5Hz), 6.96 (1H, dd, J=8.5, 2.5Hz), 4.96 (2H, s).

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Example 21(13)

4-(2-phenylsulfonylamino-4-chloro-5-methylphenoxymethyl)benzoic acid

5 [0388]

Me CI NH O2S

20

TLC : Rf 0.44 (CHCl $_3$: MeOH = 4 : 1); NMR (DMSO-d $_6$) : δ 7.91 (2H, d, J=8Hz), 7.66 (2H, d, J=7Hz), 7.55 (1H, t, J=7.5Hz), 7.47-7.30 (4H, m), 7.25 (1H, s), 6.98 (1H, s), 4.93 (2H, s), 2.23 (3H, s).

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Example 21(14)

4-(2-phenylsulfonylamino-4,5-dichlorophenoxymethyl)benzoic acid

30 **[0389**]

CI NH O2S

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35

40

TLC : Rf 0.42 (CHCl₃ : MeOH = 4 : 1); NMR (DMSO-d₆) : δ 7.92 (2H, d, J=8Hz), 7.69 (2H, d, J=7.5Hz), 7.58 (1H, t, J=7.5Hz), 7.50-7.31 (5 H, m), 7.26 (1H, s), 5.01 (2H, s).

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Example 21(15)

4-(2-phenylsulfonylamino-5-chlorophenoxymethyl)phthalic acid

5 [0390]

10 CI COOH

NH

O2S

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TLC : Rf 0.36 (CHCl $_3$: MeOH : AcOH= 15 : 4 : 1); NMR (DMSO-d $_6$) : δ 13.23 (2H, brs), 9.86 (1H, s), 7.74-7.58 (4H, m), 7.56-7.30 (4H, m), 7.29 (1H, d, J=8.5Hz), 7.06 (1H, d, J=2.0Hz), 6.98 (1H, dd, J=8.5, 2Hz), 4.94 (2H, s).

Example 21(16)

4-(2-phenylsulfonylamino-5-chlorophenoxy)benzoic acid

[0391]

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40

CI COOH

45

TLC : Rf 0.46 (CHCl₃ : MeOH = 9 : 1);

NMR: δ 7.99 (2H, d, J=9.0Hz), 7.8-7.7 (3H, m), 7.6-7.5 (1H, m), 7.5-7.3 (2H, m), 7.15 (1H, dd, J=2.2, 8.8Hz), 6.97 (1H, s), 6.77 (1H, d, J=2.2Hz), 6.65 (2H, d, J=9.0Hz).

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Reference Example 18

Methyl 4-[3-(2-nitro-5-chlorophenoxy)propyl]benzoate

(a) OH having compound

[0392]

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[0393] To a solution of methyl 4-(2-methoxycarbonylethyl)benzoate (1.0 mg) in mixture of THF-MeOH (12 ml; THF: MeOH = 5:1), sodium boron hydride (85 mg) was added. The mixture was stirred for 19 hours at room temperature. To the reaction mixture, ammonium chloride was added. After an excess of reagent was decomposed, the mixture was extracted with ethyl acetate. The organic layer was washed, dried over and concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (AcOEt: hexane = 2:3) to give the OH having compound (692 mg) having the following physical data. TLC: Rf 0.38 (hexane: AcOEt = 1:1).

(b) title compound

[0394]

CI COOMe

35

30

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[0395] To a solution of 2-nitro-5-chlorophenol (150 mg) in THF (2.0 ml), the OH having compound prepared in the above (a) (168 mg) and triphenylphosphine (227 mg) were added in a stream of argon. After then, DEAD (136 ml) was added dropwise thereto at 0°C. The reaction mixture was stirred for 24 hours at room temperature. After stirring, the mixture was quenched by adding iced water and extracted with ethyl acetate. After stirring, the mixture was quenched by adding iced water and extracted with ethyl acetate. The organic layer was washed, dried over and concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (hexane: AcOEt = 10: 15: 15: 1) to give the title compound (309 mg) having the following physical data.

TLC: Rf 0.24 (hexane: AcOEt = 5:1).

50

Example 22

4-[3-(2-phenylsulfonylamino-5-chlorophenoxy)propyf]benzoic acid

5 [0**396**]

CI O COOH

NH

O2S

20

10

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[0397] By using methyl 4-[3-(2-nitro-5-chlorophenoxy)propyl]benzoate (prepared in Reference Example 18.), the title compound having the following physical data was obtained by the same procedure as Reference Example 12—Reference Example 2—Example 2.

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TLC : Rf 0.41 (CHCl $_3$: MeOH : AcOH= 100 : 5 : 1); NMR : δ 8.04 (2H, d, J=8.4Hz), 7.73 (2H, m), 7.50 (2H, m), 7.40 (2H, m), 7.21 (2H, d, J=8.2Hz), 5.92 (1H, brs), 6.91 (1H, dd, J=2.2, 8.6Hz), 6.67 (1H, d, J=2.2Hz), 3.75 (2H, t, J=6.2Hz), 2.70 (2H, t, J=7.0Hz), 1.98 (2H, m).

30 Example 22(1)-22(4)

[0398] By using corresponding diester, halfester or 4-acetylbenzoic acid, the title compounds having the following physical data were obtained by the same procedure as Reference Example 18—Reference Example 12—Reference Example 2.

Example 22(1)

trans-4-(2-phenylsulfonylamino-5-chlorophenoxymethyl)cyclohexanoic acid

40 [0399]

CI NH O2S

55

TLC: Rf 0.39 (CHCl3: MeOH: AcOH= 100: 5:1);

NMR: 87.70 (2H, m), 7.36-7.59 (4H, m), 6.92 (1H, brs), 6.91 (1H, dd, J=2.2, 8.4Hz), 6.70 (1H, d, J=2.2Hz), 3.55

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(2H, d, J=6.2Hz), 2.31 (1H, tt, J=3.8, 12.0Hz), 2.00-2.19 (2H, m), 1.35-1.85 (5H, m), 0.95 (2H, m).

Example 22(2)

cis-4-(2-phenylsulfonylamino-5-chlorophenoxymethyl)cyclohexanoic acid

[0400]

СООН 10 15

TLC: Rf 0.53 (CHCl₃: MeOH: AcOH= 100: 5:1);

NMR: δ 7.70 (2H, m), 7.35-7.57 (4H, m), 6.89 (1H, dd, J=2.2, 8.6Hz), 6.84 (1H, brs), 6.69 (1H, d, J=2.2Hz), 3.58

(2H, d, J=6.4Hz), 2.70 (1H, m), 1.98-2.15 (2H, m), 1.43-1.80 (5H, m), 1.15-1.40 (2H, m).

Example 22(3)

6-(2-phenylsulfonylamino-5-chlorophenoxymethyl)nicotinic acid

[0401]

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COOH 028

TLC: Rf 0.40 (CHCl3: MeOH: AcOH= 100: 10: 1);

NMR (DMSO- d_6): δ 9.90 (1H, brs), 9.02 (1H, d, J=1.6Hz), 8.27 (1H, dd, J=2.2, 8.4Hz), 7.62 (2H, m), 7.49 (2H, m),

7.31-7.39 (2H, m), 7.31 (1H, d, J=8.6Hz), 7.08 (1H, d, J=2.2Hz), 7.02 (1H, dd, J=2.2, 8.6Hz), 4.96 (2H, s).

Example 22(4)

4-[1RS-(2-phenylsulfonylamino-5-chlorophenoxy)ethyl]benzoic acid

5 [0402]

10 CI COOH

NH

O2S

20

TLC: Rf 0.48 (CHCl₃: MeOH = 9:1);

NMR: 6 12.0-10.0 (1H, br), 8.00 (2H, d, J=8.4Hz), 7.78 (2H, d, J=7.8Hz), 7.7-7.4 (4H, m), 7.1-7.0 (3H, m), 6.88 (1H, dd, J=2.2, 8.8Hz), 6.45 (1H, s), 5.14 (1H, q, J=6.4Hz), 1.50 (3H, d, J=6.4Hz).

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Reference Example 19

2-nitro-5-trifluoromethylphenyl methoxymethyl ether

30 [0403]

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[0404] To a solution of 2-nitro-5-trifluoromethylphenol (400 mg) in DMF (4.0 ml), sodium hydride (77 mg) was added at 0°C in a stream of argon. The mixture was stirred for 30 minutes After stirring, methoxymethyl chloride (147 ml) was added dropwise thereto. The mixture was stirred for 20 minutes. The reaction mixture was quenched by iced water and extracted with ethyl acetate. The layer containing ethyl acetate was washed, dried over and concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (hexane: AcOEt = 20:1) to give the title compound (353 mg) having the following physical data.

TLC: Rf 0.44 (hexane: AcOEt = 10:1).

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Reference Example 20

2-amino-5-trifluoromethylphenyl methoxymethyl ether

[0405]

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[0406] To a solution of 2-nitro-5-trifluoromethylphenyl methoxymethyl ether (353 mg; prepared in Reference Example 19.) in MeOH (3.5 ml), 10%Pd-C (30 mg) was added in a stream of argon. The mixture was stirred vigorously at room temperature under hydrogen atmosphere. The reaction mixture was filtered through celite and concentrated under the reduced pressure to give the title compound (313 mg) having the following physical data.

TLC: Rf 0.44 (hexane: AcOEt = 3:1).

Reference Example 21

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Methyl N-(2-methoxymethoxy-4-trifluoromethylphenyl)-phenylsulfonylaminoacetate

[0407]

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[0408] By using 2-amino-5-trifluoromethylphenyl methoxymethyl ether (313 mg; prepared in Reference Example 20.), the title compound (625 mg) having the following physical data was obtained by the same procedure as Reference Example 2-Example 17.

TLC: Rf 0.66 (benzene: acetone = 9:1).

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Reference Example 22

1,1-dimethyl-2-[N-(2-methoxymethoxy-4-trifluoromethylphenyl)-phenylsulfonylamino]ethanol

5 **[0409**]

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F₃C O OMe O₂S O H

[0410] To a solution of methyl N-(2-methoxymethoxy-4-trifluoromethylphenyl)-phenylsulfonylaminoacetate (525 mg; prepared in Reference Example 21.) in THF (6.0 ml), methylmagnesium bromide (2.67 ml) was added dropwise in a stream of argon at 0°C. The mixture was stirred for 30 minutes. The reaction mixture was quenched by iced water, extracted with ethyl acetate, washed, dried over and concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (hexane : AcOEt = 2 : 1) to give the title compound (380 mg) having the following physical data. TLC : Rf 0.26 (hexane : AcOEt = 2 : 1).

Reference Example 23

1,1-dimethyl-2-[N-(2-hydroxy-4-trifluoromethylphenyl)-phenylsulfonylamino]ethanol

[0411]

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F₃C OH OH

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[0412] To a solution of 1,1-dimethyl-2-[N-(2-methoxymethoxy-4-trifluoromethylphenyl)-phenylsulfonylamino]ethanol (380 mg; prepared in Reference Example 22.) in THF (4.0 ml), 6N HCl (0.8 ml) was added. The mixture was stirred for 2 days at room temperature. The reaction mixture was diluted with ethyl acetate, washed, dried over and concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (hexane: AcOEt = 2:1) to give the title compound (291 mg) having the following physical data.

TLC: Rf 0.29 (benzene: acetone = 9:1).

Referenc Example 24

2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenol

[0413]

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F₃C OH OH

[0414] By using 2-amino-5-trifluoromethylphenyl methoxymethyl ether (prepared in Reference Example 20.), the title compound having the following physical data was obtained by the same procedure as Reference Example 2→Example 17→Reference Example 23.

TLC: Rf 0.57 (hexane: AcOEt = 5:2).

Example 23

4-[2-[N-(2-hydroxy-2-methylpropyl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid

30 [0415]

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[0416] By using 1,1-dimethyl-2-[N-(2-hydroxy-4-trifluoromethylphenyl)-phenylsulfonylamino]ethanol (prepared in Reference Example 23.), the title compound having the following physical data was obtained by the same procedure as Reference Example 6—Example 2.

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TLC : Rf 0.48 (CHCl₃ : MeOH : AcOH= 100 : 5 : 1); NMR (CD₃COCD₃) : δ 8.03 (2H, brd, J=8.2Hz), 7.47-7.66 (4H, m), 7.30-7.47 (6H, m), 5.21 (1H, m), 4.89 (1H, m), 3.79 (2H, s), 1.20 (6H, s).

55 Example 23(1)-23(3)

[0417] By using 2-[N-(2-hydroxy-2-methylpropyl)-phenylsulfonylamino]-5-trifluoromethylphenol (prepared in R ference Example 23.), the title compounds having the following physical data were obtained by the same procedure as

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Reference Example 6→Example 2.

Example 23(1)

4-[2-[N-(2-hydroxy-2-methylpropyi)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]cinnamic acid

[0418]

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TLC: Rf 0.53 (CHCl₃: MeOH = 9:1);

NMR: δ 7.80 (1H, d, J=16.0Hz), 7.54 (6H, m), 7.35 (6H, m), 6.49 (1H, d, J=16.0Hz), 4.99 (1H, m), 4.81 (1H, m), 3.63 (2H, m), 1.21 (6H, s).

Example 23(2)

30 4-[2-[N-(2-hydroxy-2-methylpropyl)-phenylsulfonylamino]-5-methylphenoxymethyl]benzoic acid

[0419]

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TLC: Rf 0.45 (CHCl₃: MeOH = 9:1);

50 NMR: 8 8.09 (2H, d, J=8.4Hz), 7.60 (2H, m), 7.28-7.44 (5H, m), 7.06 (1H, m), 6.71 (2H, m), 5.00 (1H, d, J=12.8Hz), 4.74 (1H, d, J=12.8Hz), 3.69 (1H, d, J=14.2Hz), 3.57 (1H, d, J=14.2Hz), 2.33 (3H, s), 2.13 (1H, s), 1.25 (3H, bs), 1.19 (3H, bs).

Example 23(3)

4-[2-[N-(2-hydroxy-2-methylpropyl)-2-furanylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid

5 **[0420**]

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TLC: Rf 0.42 (CHCl3: MeOH = 9:1);

NMR : δ 8.15 (2H, d, J=8.4Hz), 7.52 (2H, d, J=8.4Hz), 7.21-7.34 (4H, m), 6.82 (1H, m), 6.38 (1H, m), 5.12 (2H, m), 3.76 (2H, m), 2.12 (1H, s), 1.23 (6H, bs).

Example 24

4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]phenoxy acetic acid

30 [0421]

F₃C O COOH

45

[0422] By using 2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenol (prepared in Reference Example 24.), the title compound having the following physical data was obtained by the same procedure as Reference Example 18 (b)—Example 2.

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TLC: Rf 0.39 (AcOEt: hexane: AcOH= 9: 10: 1); NMR: δ 7.80 (2H, d, J=7.5Hz), 7.49 (1H, t, J=7.5Hz), 7.40-7.20 (7H, m), 6.95 (2H, d, J=8.5Hz), 4.98 (2H, s), 4.72 (2H, s), 4.28 (1H, qn, J=6.5Hz), 1.06 (3H, d, J=6.5Hz), 1.01 (3H, d, J=6.5Hz).

55 Example 24(1)-24(10)

[0423] By using the corresponding compounds, the title compounds having the following physical data were obtained by the same procedure as Reference Example 18 (b)—Example 2.

Example 24(1)

 $5\hbox{-}[2\hbox{-}(N\hbox{-}isopropyl\hbox{-}phenylsulfonylamino})\hbox{-}5\hbox{-}trifluoromethylphenoxymethyl] thiophene-2\hbox{-}carboxylic acid$

[0424]

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СООН

20 TLC: Rf 0.54 (CHCl3: MeOH: AcOH= 90:9:1);

NMR: δ 7.9-7.7 (3H, m), 7.6-7.3 (3H, m), 7.3-7.2 (3H, m), 7.16 (1H, d, J=4.0Hz), 5.20 (2H, s), 4.5-4.3 (1H, m), 1.10

(3H, d, J=3.8Hz), 1.32 (3H, d, J=3.8Hz).

25 Example 24(2)

 $5\hbox{-}[2\hbox{-}(N\hbox{-}isopropyl\hbox{-}phenylsulfonylamino})\hbox{-}5\hbox{-}trifluoromethylphenoxymethyl] furan-2\hbox{-}carboxylic acid$

[0425]

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СООН

45 TLC: Rf 0.17 (CHCl₃: MeOH = 5:1);

NMR: δ 7.76 (2H, d, J=8Hz), 7.54-7.29 (3H, m), 7.29-7.13 (4H, m), 6.52 (1H, m), 5.00 (2H, s), 4.31 (1H, m), 0.98 (6H, m).

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Example 24(3)

4-[2-(N-isopropyl-phenylsulfonylamino)-5-methylphenoxymethyl]phenoxyacetic acid

[0426]

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COOH

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TLC: Rf 0.09 (AcOEt);

NMR: δ 7.81 (2H, d, J=7.5 Hz), 7.50-7.30 (5H, m), 7.00-6.91 (3H, m), 6.82-6.73 (2H, m), 4.91 (2H, s), 4.71 (2H, s), 4.27 (1H, sept, J=7Hz), 2.36 (3H, s), 1.05 (3H, d, J=7Hz), 1.01 (3H, d, J=7Hz).

Example 24(4)

5-[2-(N-isopropyl-phenylsulfonylamino)-5-methylphenoxymethyl]thiophene-2-carboxylic acid

30 [0427]

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СООН

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TLC: Rf 0.30 (CHCl₃: MeOH = 9:1);

NMR: δ 7.9-7.7 (3H, m), 7.5-7.4 (1H, m), 7.4-7.3 (2H, m), 7.12 (1H, d, J=3.6Hz), 7.01 (1H, d, J=8.2Hz), 6.9-6.7

(2H, m), 5.12 (2H, s), 4.5-4.3 (1H, m), 2.38 (3H, s), 1.51 (3H, d, J=2.4Hz), 1.05 (3H, d, J=2.4Hz).

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Example 24(5)

4-[2-(N-isopropyl-phenylsulfonylamino)-5-methylphenoxymethyl]cinnamic acid

5 **[0428]**

Me COOH

O2S

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TLC: Rf 0.39 (hexane: AcOEt = 1:2);

NMR : δ 7.86-7.78 (3H, m), 7.60-7.26 (7H, m), 6.97 (1H, d, J=8Hz), 6.80-6.74 (2H, m), 6.48 (1H, d, J=16Hz), 5.01 (2H, s), 4.36 (1H, sept., J=6.5Hz), 1.05 (6H, d, J=6.5Hz).

Example 24(6)

4-[2-(N-isopropyl-phenylsulfonylamino)-5-chlorophenoxymethyl]phenoxyacetic acid

30 [0429]

CI O COOH

45

TLC: Rf 0.10 (CHCl₃: MeOH = 10:1);

NMR: δ 7.80-7.76 (2H, m), 7.52-7.44 (1H, m), 7.35-7.26 (4H, m), 7.05-6.91 (5H, m), 4.91 (2H, s), 4.72 (2H, s), 4.28 (1H, sept., J=7Hz), 1.05 (3H, d, J=7Hz), 1.00 (2H, d, J=7Hz).

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Example 24(7)

4-[2-(N-isopropyl-phenylsulfonylamino)-5-chlorophenoxymethyl]cinnamic acid

[0430]

COOH 10 15

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TLC: Rf 0.31 (hexane: AcOEt = 1:1);

NMR: δ 7.85-7.77 (2H, m), 7.60-7.35 (7H, m), 7.05-6.90 (3H, m), 6.48 (1H, d, J=16Hz), 5.01 (2H, s), 4.36 (1H,

sept., J=6.5Hz), 1.04 (6H, d, J=7Hz).

Example 24(8)

5-[2-(N-isopropyl-phenylsulfonylamino)-5-chlorophenoxymethyl]thiophene-2-carboxylic acid

[0431]

COOH

45

TLC: Rf 0.42 (CHCl₃: MeOH = 9:1);

NMR : δ 7.8-7.7 (3H, m), 7.5-7.3 (3H, m), 7.2-6.9 (4H, m), 5.15 (1H, d, J=13.2Hz), 5.08 (1H, d, J=13.2Hz), 4.5-4.3

(1H, m), 5.5-4.0 (1H, br), 1.08 (3H, d, J=2.6Hz), 1.05 (3H, d, J=2.6Hz).

55

Example 24(9)

5-[2-(N-isopropyl-phenylsulfonylamino)-5-chlorophenoxymethyl]furan-2-carboxylic acid

5 **[0432]**

10 CI COOH
O25

TLC : Rf 0.37 (CHCl₃ : MeOH = 9 : 1);

NMR : δ 7.9-7.7 (2H, m), 7.6-7.4 (3H, m), 7.31 (1H, d, J=3.4Hz), 7.0-6.9 (3H, m), 6.63 (1H, d, J=3.4Hz), 5.03 (1H, d, J=13.2Hz), 4.96 (1H, d, J=13.2Hz), 5.5-4.5 (1H, br), 4.4-4.2 (1H, m), 1.03 (6H, d, J=6.6Hz).

25 Example 24(10)

4-[2-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxy]ethyl]benzoic acid

[0433]

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TLC : Rf 0.40 (CHCl $_3$: MeOH = 9 : 1);

NMR: δ 8.07 (2H, d, J=8.5Hz), 7.83 (2H, d, J=7Hz), 7.65-7.45 (5H, m), 7.39 (2H, d, J=8.5Hz), 7.25-7.08 (3H, m), 4.37 (1H, m), 4.25-4.05 (2H, m), 3.08 (2H, d, J=7Hz), 0.99 (3H, d, J=6.5Hz), 0.84 (3H, d, J=6.5Hz).

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Example 25

2-methoxy-4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0434]

F₃C OMe
O₂S
O₂S

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[0435] By using 2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenol (prepared in Reference Example 24.), the title compound having the following physical data was obtained by the same procedure as Reference Example 6—Example 2.

TLC: Rf 0.49 (CHCl₃: MeOH = 9: 1);

NMR: δ 11.0-10.6 (1H, br), 8.21 (1H, d, J=7.8Hz), 7.9-7.8 (2H, m), 7.71 (1H, d, J=0.6Hz), 7.7-7.4 (3H, m), 7.3-7.2 (2H, m), 7.2-7.1 (1 H, m), 7.00 (1H, d, J=7.8Hz), 5.22 (2H, s), 4.6-4.4 (1H, m), 4.18 (3H, s), 1.08 (3H, d, J=6.6Hz), 0.92 (3H, d, J=6.6Hz).

Example 26

2-hydroxy-4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0436]

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[0437] By using 2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenol (prepared in Reference Example 24.), the title compound having the following physical data was obtained by the same procedure as Reference Example 6—Reference Example 23—Example 2.

TLC: Rf 0.56 (CHCl₃: MeOH: AcOH= 90:9:1);

NMR: δ 10.51 (1H, s), 7.95 (1H, d, J=8.0Hz), 7.9-7.8 (2H, m), 7.6-7.4 (3H, m), 7.3-7.2 (3H, m), 7.1-7.0 (2H, m),

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5.05 (2H, s), 4.5-4.3 (1H, m), 1.09 (3H, d, J=5.0Hz), 1.06 (3H, d, J=5.0Hz).

Example 26(1)-26(2)

5 [0438] By using the corresponding compounds, the title compounds having the following physical data were obtained by the same procedure as Reference Example 6→Reference Example 23→Example 2.

Example 26(1)

2-hydroxy-4-[2-(N-isopropyl-phenylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

[0439]

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TLC: Rf 0.20 (CHCl₃: MeOH = 17:3);

NMR: 8 10.50 (1H, s), 7.92 (1H, d, J=8.5Hz), 7.83 (2H, m), 7.54-7.32 (3H, m), 7.05-6.93 (3H, m), 6.81-6.72 (2H, m), 4.97 (2H, s), 4.42 (1H, m), 2.35 (3H, s), 1.13-0.98 (6H, m).

Example 26(2)

³⁵ 2-hydroxy-4-[2-(N-isopropyl-phenylsulfonylamino)-5-chlorophenoxymethyl]benzoic acid

[0440]

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TLC: Rf 0.21 (CHCl₃: MeOH = 9:1);

NMR: δ 7.93 (1H, d, J=8.0Hz), 7.9-7.7 (2H, m), 7.6-7.3 (3H, m), 7.1-6.9 (5H, m), 4.97 (2H, s), 4.5-4.3 (1H, m), 3.0-2.0 (2H, br), 1.07 (3H, d, J=6.2Hz), 1.04 (3H, d, J=6.2Hz).

Reference Example 25

4-phenylsulfonylamino-3-nitrobenzotrifluoride

[0441]

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F₃C NO₂
NH
O₂S

[0442] To a solution of 4-amino-3-nitrobenzotrifluoride (3.09 g) in THF sodium hydride (660 mg) was added. The mixture was stirred for 30 minutes at room temperature. After stirring, benzenesulfonylchloride (3.18 g) was added thereto. The mixture was stirred for 2 hours at room temperature. In addition, sodium hydride (420 mg) was added thereto. The mixture was stirred for 1 hour. The reaction mixture was acidified by adding an aqueous solution of ammonium chloride and extracted with ethyl acetate. The organic layer was washed, dried over, filtered and concentrated to give the title compound (4.86 g) having the following physical data.

TLC: Rf 0.31 (hexane: AcOEt = 3:1).

Reference Example 26

4-phenylsulfonylamino-3-aminobenzotrifluoride

[0443]

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[0444] By using 4-phenylsulfonylamino-3-nitrobenzotrifluoride (2.4 g; prepared in Reference Example 25.), the title compound (1.7 g) having the following physical data was obtained by the same procedure as Reference Example 12.

TLC: Rf 0.17 (hexane: AcOEt = 3:1).

Example 27

Methyl 4-(2-phenylsulfonylamino-5-trifluoromethylphenylaminomethyl)benzoate

[0445]

COOMe 15

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[0446] To a solution of 4-phenylsulfonylamino-3-aminobenzotrifluoride (100 mg; prepared in Reference Example 26.) and terephthal aldehyde acid methyl ester (78 mg) in MeOH (2 ml), acetic acid (1.5 ml) was added. The mixture was stirred for 2 hours at room temperature. After stirring, a solution of sodium cyanoborohydride (30 mg) in MeOH (2 ml) 25 was added. The mixture was stirred for 2 hours at room temperature. The reaction solution was extracted with H₂O-AcOEt, washed, dried over, filtered and concentrated. The precipitate was washed with hexane to give the title compound (146 mg) having the following physical data.

TLC: Rf 0.27 (hexane: AcOEt = 2:1); NMR: 88.02 (2H, m), 7.76 (2H, m), 7.6-7.4 (5H, m), 6.74-6.70 (2H, m), 6.55-6.50 (1H, m), 6.02 (1H, bs), 5.35 (1H, m), 4.40 (2H, m), 3.92 (3H, s).

Example 28

4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenylaminomethyl]benzoic acid

[0447]

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[0448] By using methyl 4-(2-phenylsulfonylamino-5-trifluoromethylphenylaminomethyl)benzoate (prepared in Exam-55 ple 27.), the title compound having the following physical data was obtained by the same procedure as Example 17→Example 2.

TLC: Rf 0.45 (hexane: AcOEt = 1:1);

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NMR : δ 8.10 (2H, d, J=8.5 Hz), 7.8-7.7 (2H, m), 7.6-7.4 (5H, m), 6.8-6.7 (2H, m), 6.7-6.6 (1H, m), 5.34 (1H, m), 4.69 (1H, sept, J=7 Hz), 4.45 (2H, d, J=6 Hz), 1.15 (3H, d, J=7Hz), 1.01 (3H, d, J=7Hz).

Example 29

Methyl 4-[N-methyl-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenyl]aminomethyl]benzoate

[0449]

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F₃C Me COOMe

O₂S

[0450] Methyl 4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenylaminomethyl]benzoate (200 mg) prepared by the same procedure as Example 17 by using methyl 4-(2-phenylsulfonylamino-5-trifluoromethylphenylaminomethyl)benzoate (prepared in Example 27.) was dissolved in DMF (5 ml). Sodium hydride (64 mg) and methyl iodide (200 ml) were added thereto. The mixture was stirred for 24 hours at 60°C. The reaction mixture was extracted with H₂O-AcOEt, washed, dried over, filtered and concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (hexane : AcOEt = 5 : 1) to give the title compound (105 mg) having the following physical data.

TLC: Rf 0.54 (CH2Cl2);

NMR : δ 8.0 (2H, m), 7.9 (2H, m), 7.6-7.5 (3H, m), 7.4 (2H, m), 7.4-7.2 (2H, m), 7.0 (1H, m), 4.6-4.3 (2H, m), 3.92 (3H, m), 2.72 (3H, s), 1.2 (3H, m), 0.8 (3H, m).

Example 30

4-[N-methyl-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenyl]aminomethyl]benzoic acid

5 **[0451]**

F₃C Me COOH

20

[0452] By using methyl 4-[N-methyl-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenyl]aminomethyl]benzoate (prepared in Example 29.), the title compound having the following physical data was obtained by the same procedure as Example 2.

TLC : Rf 0.45 (hexane : AcOEt = 1 : 1); NMR : δ 8.09 (2H, d, J=8 Hz), 7.9 (2H, m), 7.7-7.4 (5H, m), 7.2 (2H, m), 7.0 (1H, m), 4.6-4.4 (3H, m), 2.75 (3H, s), 1.26 (3H, d, J=7Hz), 0.85 (3H, d, J=7Hz).

30

Reference Example 27

Methyl 2-t-butoxycarbonylamino-5-trifluoromethylbenzoate

35 [0453]

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[0454] 4-t-butoxycarbonylaminobenzotrifluoride (3.90 g) was dissolved in THF. At -50°C, t-butyl lithium (30 ml) was added dropwise thereto. The mixture was stirred for 3 hours with keeping at -50°C. Carbon dioxide gas was bubbled into this mixture under stirring (the temperature increased to about -30°C.). The solvent was distilled out. The back-extractraction of the residue with 2N NaOH-ether mixture solution was carried out. The aqueous layer was acidified by adding 2N HCl, extracted with ether, washed and dried over. In addition, the layer containing ether was washed, dried over, filtered and concentrated after combining the said layer containing ether to give the crude compound. Such crude compound was dissolved in ether. A solution of diazomethane in ether was added thereto until the reaction solution became yellow. The reaction solution was concentrated and purified on silica gel column chromatography (hexane:
 AcOEt = 20 : 1 10 : 1) to give the title compound (3.80 g) having the following physical data.

TLC: Rf 0.70 (hexane: AcOEt = 3:1).

Reference Example 28

Methyl 2-amino-5-trifluoromethylbenzoate

[0455]

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[0456] To a solution of methyl 2-t-butoxycarbonylamino-5-trifluoromethylbenzoate (3.80 g; prepared in Reference Example 27.) in methylene chloride (30 ml), trifluoroacetic acid (6 ml) was added. The mixture was stirred for 8 hours at room temperature. The solvent was distilled off azeotropically with toluene three times. To the reaction mixture, an aqueous sodium hydrogencarbonate solution was added to neutralize. The mixture was extracted with ethyl acetate, washed, dried, filtered and concentrated under the reduced pressure. The residue was purified on silica get column chromatography (hexane: AcOEt = 5:1) to give the title compound (2.35 g) having the following physical data.

TLC: Rf 0.20 (hexane: AcOEt = 5:1).

Example 31

4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylbenzoylamino]benzoic acid

[0457]

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[0458] By using methyl 2-amino-5-trifluoromethylbenzoate (prepared in Reference Example 28.), the title compound having the following physical data was obtained by the same procedure as Reference Example 2→Reference Example 3→Example 1→Example 2.

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TLC: Rf 0.25 (hexane: AcOEt = 1:2);

J=6.5Hz), 0.86 (3H, d, J=6.5Hz).

Reference Example 29

Methyl 4-[2-[N-[1,3-bis(t-butyldimethylsilyloxy)prop-2-yl]-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoate

(a) 1,3-diOTBs having compound (intermediate)

[0459]

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5

TBsQ OH

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[0460] To a solution of glycerol (2 g) in DMF (15 ml), solution of t-butyldimethylsilylchloride (6.5 g) and imidazole (3.3 g) in DMF (8 ml) was added dropwise slowly at 0°C. The solution was stirred for 3 hours at room temperature. The reaction mixture was poured into water, extracted with AcOEt-hexane (AcOEt: hexane = 1:1) mixture solution and purified on silica gel column chromatography to give the 1,3-diOTBs having compound (5.8 g) having the following physical data. TLC: Rf 0.5 (hexane: AcOEt = 9:1).

25 (b) title compound

[0461]

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F₃C OOMe

OTBs

O₂S

OTBs

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[0462] By using methyl 4-(2-phenylsulfonylamino-5-trifluoromethylphenoxymethyl)benzoate (180 mg; prepared in Example 15.) and the 1,3-diOTBS having compound prepared in the above (a) (247 mg), the title compound (200 mg) having the following physical data was obtained by the same procedure as Example 19.

TLC: Rf 0. 28 (hexane: AcOEt = 9:1).

50

Methyl 4-[2-[N-(1,3-dihydroxyprop-2-yl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoate

[0463]

F₃C O H O₂S O H

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[0464] To a solution of methyl 4-[2-[N-[1,3-bis(t-butyldimethylsilyloxy)prop-2-yl]-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoate (200 mg; prepared in Reference Example 29.) in THF (3 ml), a solution of tetrabutylanmonimu fluoride (0.57 ml) in THF (1M) was added. The solution was stirred for 3 hours at room temperature. To the reaction compound, water was added. The mixture was extracted with ethyl acetate, washed, dried over and purified on silica gel column chromatography (110 mg) having the following physical data.

TLC: Rf 0.50 (CH_2Cl_2 : MeOH = 9:1);

NMR : δ 8.08 (2H, d, J=8.2Hz), 7.78 (2H, d, J=7.2Hz), 7.70-7.24 (8H, m), 5.14 (1H, d, J=12.0Hz), 5.06 (1H, d, J=12.0Hz), 4.50-4.30 (1H, m), 3.93 (3H, s), 3.80-3.20 (4H, m), 2.72 (1H, dd, J=3.6, 18.2Hz).

Example 33

4-[2-[N-(1,3-dihydroxyprop-2-yl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid

[0465]

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[0466] By using methyl 4-[2-[N-(1,3-dihydroxyprop-2-yl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoate (prepared in Example 32.), the title compound having the following physical data was obtained by the same procedure as Example 2.

TLC: Rf 0.51 (AcOEt: AcOH≈ 99:1);

NMR: δ 8.13 (2H, d, J=8.4Hz), 7.8-7.7 (2H, m), 7.6-7.2 (8H, m), 5.17 (1H, d, J=11.4Hz), 5.08 (1H, d, J=11.4Hz),

4.5-4.3 (1H, m), 3.6-3.5 (2H, m), 3.4-3.2 (2H, m).

Example 34

4-[2-[N-(1,3-dimethoxyprop-2-yl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid

[0467]

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F₃C OMe OMe O₂S OMe

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[0468] By using methyl 4-[2-[N-(1,3-dihydroxyprop-2-yl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoate (prepared in Example 32.), the title compound having the following physical data was obtained by the came procedure as Reference Example 19—Example 2.

TLC: Rf 0.57 (CHCl₃: MeOH = 9:1);

NMR : δ 8.18 (2H, d, J=8.2Hz), 7.8-7.7 (2H, m), 7.63 (2H, d, J=8.2Hz), 7.6-7.4 (3H, m), 7.3-7.2 (3H, m), 5.18 (2H, s), 4.5-4.4 (1H, m), 3.7-3.6 (1H, m), 3.5-3.0 (3H, m), 3.09 (3H, s), 3.04 (3H, s).

Reference Example 30

2-(N-isopropyl-methylsulfonylamino)-5-trifluoromethylphenyl methoxymethyl ether

[0469]

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F₃C O OMe

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[0470] By using 2-amino-5-trifluoromethylphenyl methoxymethyl ether and mesylchloride, the title compound having the following physical data was obtained by the same procedure as Reference Example 2->Example 17.

TLC: Rf 0.40 (hexane: AcOEt = 2:1).

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2-(N-isopropyl-2-hydroxyhexylsulfonylamino)-5-trifluoromethylphenyl methoxymethyl ether

[0471]

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[0472] To a solution of 2-(N-isopropyl-methylsulfonylamino)-5-trifluoromethylphenyl methoxymethyl ether (135 mg; prepared in Reference Example 30.) in THF (3.0 ml), hexamethylphosphoramide (420 ml) was added in a stream of argon. At -78°C, n-butyl lithium (742 ml) was added dropwise thereto. The mixture was stirred for 1.5 hours. To the mixture, a solution of valeraldehyde (102 mg) in THF (1.0 ml) was added dropwise. The mixture was stirred for 30 minutes. To the reaction mixture, water was added. The mixture was extracted with ethyl acetate, washed, dried over and concentrated with the reduced pressure. The residue was purified on silica gel column chromatography (hexane: AcOEt = 4:1) to give the title compound (69 mg) having the following physical data.

25

TLC: Rf 0.49 (hexane: AcOEt = 2:1).

Reference Example 32

30 2-(N-isopropyl-1-hexenylsulfonylamino)-5-trifluoromethylphenyl methoxymethyl ether

[0473]

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[0474] To a solution of 2-(N-isopropyl-2-hydroxyhexylsulfonylamino)-5-trifluoromethylphenyl methoxymethyl ether (160 mg; prepared in Reference Example 31.) in methylene chloride (2.0 ml), triethylamine(104 ml) and mesylchloride (35 ml) were added in a stream of argon at 0°C. The mixture was stirred for 10 minutes. To the mixture, 1,5-diazabicy-clo[5,4,0]undecene (134 ml) was added. The mixture was stirred for 2 hours at room temperature. To the reaction mixture, diluted HCl was added. The mixture was extracted with ethyl acetate, washed, dried over and concentrated with the reduced pressure. The residue was purified on silica gel column chromatography (hexane : AcOEt = 8 : 1) to give the title compound (140 mg) having the following physical data.

TLC: Rf 0.37 (hexane: AcOEt = 3:1).

4-[2-(N-isopropyl-1-hexenylsulfonylamino)-5-trifluoromethylphenoxymethyllbenzoic acid

5 **[0475]**

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F₃C COOH

[0476] By using 2-(N-isopropyl-1-hexenylsulfonylamino)-5-trifluoromethylphenyl methoxymethyl ether (prepared in Reference Example 32.), the title compound having the following physical data was obtained by the same procedure as Reference Example 23—Reference Example 6—Example 2.

TLC: Rf 0.44 (CHCl₃: MeOH: AcOH= 100: 5:1);
NMR: δ 8.19 (2H, d, J=8.2Hz), 7.62 (2H, d, J=8.2Hz), 7.22-7.45 (3H, m), 6.68 (1H, td, J=7.0, 15.0Hz), 6.09 (1H, td, J=1.4, 15.0Hz), 5.19 (2H, s), 4.15 (1H, m), 1.97 (2H, m), 1.16-1.40 (7H, m), 1.03 (3H, d, J=6.8Hz), 0.86 (3H, m).

Reference Example 33

Methyl 4-(2-cyclopentylsulfinylamino-5-trifluoromethylphenoxymethyl)benzoate

[0477]

F₃C COOMe

50 [0478] To a solution of methyl 4-(2-amino-5-trifluoromethylphenoxymethyl)benzoate (300 mg) in methylene chloride (3.0 ml), pyridine (187 ml) and triphenylphosphine (315 mg) were added in a stream of argon. At 0°C, cyclopentylsulfonylchloride (202 mg) was added dropwise thereto. The mixture was stirred for 6 hours at room temperature. To the reaction mixture water was added. The mixture was extracted with ethyl acetate, washed, dried over and concentrated with the reduced pressure. The residue was purified on silica gel column chromatography (hexane: AcOEt = 2:11:1) to give the title compound (309 mg) having the following physical data.

TLC: Rf 0.23 (hexane: AcOEt = 2:1).

Methyl 4-(2-cyclopentylsulfonylamino-5-trifluoromethylphenoxymethyl)benzoate

5 [0479]

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[0480] To a solution of methyl 4-(2-cyclopentylsulfinylamino-5-trifluoromethylphenoxymethyl)benzoate (305 mg; prepared in Reference Example 33.) in methylene chloride (4.0 ml), meta-chloroperbenzoic acid (456 mg) was added at 0°C. The mixture was stirred for 1 hour. The reaction mixture was diluted with ethyl acetate, washed, dried over and concentrated under the reduced pressure to give the title compound (317 mg) having the following physical data.

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TLC: Rf 0.56 (hexane: AcOEt = 2:1);

NMR: δ 8.11 (2H, d, J=8.6Hz), 7.73 (1H, brd, J=9.0Hz), 7.47 (2H, d, J=8.6Hz), 7.25 (1H, m), 7.15 (1H, d, J=1.4Hz), 6.95 (1H, brs), 5.21 (2H, s), 3.95 (3H, s), 3.54 (1H, m), 1.53-2.16 (8H, m).

30 Example 37

4-[2-(N-isopropyl-cyclopentylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0481]

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[0482] By using methyl 4-(2-cyclopentylsulfonylamino-5-trifluoromethylphenoxymethyl)benzoate (prepared in Example 36.), the title compound having the following physical data was obtained by the same procedure as Example 17—Example 2.

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TLC: Rf 0.40 (CHCl₃: MeOH: AcOH= 100: 5:1); NMR: δ 8.17 (2H, d, J=8.4Hz), 7.61 (2H, d, J=8.4Hz), 7.38 (1H, d, J=8.0Hz), 7.28 (2H, m), 5.17 (2H, s), 4.36 (1H, sept, J=6.6Hz), 3.51 (1H, m), 1.84-2.10 (3H, m), 1.61-1.84 (3H, m), 1.30-1.56 (2H, m), 1.24 (3H, d, J=6.6Hz), 1.08 (3H, d, J=6.6Hz).

Example 37(1)-37(7)

[0483] By using the corresponding compounds, the title compounds having the following physical data were obtained by the same procedure as Reference Example 33—Example 36—Example 17—Example 2.

Example 37(1)

4-[2-(N-isopropyl-cyclohexylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

10 [0484]

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F₃C COOH

TLC: Rf 0.27 (AcOEt: hexane = 1:1);

NMR : δ 8.17 (2H, d, J=8Hz), 7.61 (2H, d, J=8Hz), 7.42 (1H, d, J=8Hz), 7.28 (1H, d, J=8Hz), 7.26 (1H, s), 5.19 (2H, s), 4.32 (1H, m), 2.88 (1H, m), 2.25-2.04 (2H, m), 1.92-1.35 (5H, m), 1.30-0.60 (9H, m).

30 Example 37(2)

4-[2-(N-isopropyl-cyclohexylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

[0485]

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Me O₂S COOH

50 TLC: Rf 0.37 (CHCl₃: MeOH: AcOH= 100: 5:1);

NMR: δ 8.15 (2H, d, J=8.6Hz), 7.59 (2H, d, J=8.6Hz), 7.17 (1H, d, J=8.4Hz), 6.82 (2H, m), 5.13 (2H, s), 4.32 (1H, m), 2.88 (1H, tt, J=3.2, 12.0Hz), 2.35 (3H, s), 2.15 (2H, m), 1.36-1.90 (5H, m), 1.23 (3H, d, J=6.6Hz), 1.12 (3H, d, J=6.6Hz), 0.82 (1H, m).

Example 37(3)

4-[2-(N-isopropyl-isopropylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0486]

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F₃C O COOH

20 TLC: Rf 0.34 (CHCl₃: MeOH: AcOH= 100:5:1);

NMR: δ 8.18 (2H, d, J=8.4Hz), 7.60 (2H, d, J=8.4Hz), 7.42 (1H, d, J=8.0Hz), 7.23-7.33 (2H, m), 5.17 (2H, s), 4.32 (1H, sept, J=6.6Hz), 3.17 (1H, sept, J=7.0Hz), 1.32 (3H, d, J=7.0Hz), 1.25 (3H, d, J=6.6Hz), 1.19 (3H, d, J=7.0Hz), 1.09 (3H, d, J=6.6Hz).

Example 37(4)

4-[2-(N-isopropyl-isopropylsulfonylamino)-5-methylphenoxymethyl]benzoic acid

30 [0487]

Me COOH

TLC: Rf 0.46 (CHCl3: MeOH: AcOH= 100: 5:1);

NMR: δ 8.15 (2H, d, J=8.2Hz), 7.57 (2H, d, J=8.2Hz), 7.16 (1H, d, J=8.4Hz), 6.81 (2H, m), 5.11 (2H, s), 4.31 (1H, sept, J=6.6Hz), 3.16 (1H, sept, J=6.8Hz), 2.36 (3H, s), 1.31 (3H, d, J=6.8Hz), 1.23 (3H, d, J=6.6Hz), 1.18 (3H, d, J=6.6Hz), 1.08 (3H, d, J=6.8Hz).

Example 37(5)

4-[2-(N-isopropyl-isopropylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

[0488]

10 F₃C COOH

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TLC: Rf 0.20 (AcOEt: hexane = 1:1);

NMR : δ 7.79 (1H, d, J=15Hz), 7.61 (2H, d, J=8Hz), 7.50 (2H, d, J=8Hz), 7.40 (1H, d, J=8Hz), 7.34-7.20 (2H, m), 6.48 (1H, d, J=15Hz), 5.12 (2H, s), 4.31 (1H, m), 3.14 (1H, m), 1.31 (3H, d, J=7Hz), 1.25 (3H, d, J=7Hz), 1.15 (3H, d, J=7Hz), 1.07 (3H, d, J=7Hz).

Example 37(6)

4-[2-(N-isopropyl-cyclopentylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

[0489]

F₃C COOH

45

TLC: Rf 0.24 (AcOEt: hexane = 1:1);

NMR : δ 7.80 (1H, d, J=15Hz), 7.61 (2H, d, J=8Hz), 7.53 (2H, d, J=8Hz), 7.38 (1H, d, J=8Hz), 7.30-7.22 (2H, m), 6.48 (1H, d, J=15Hz), 5.13 (2H, s), 4.35 (1H, m), 3.49 (1H, m), 2.20-1.16 (11H, m), 1.07 (3H, d, J=7Hz).

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Example 37(7)

 $\hbox{$4$-[2-(N-isopropyl-cyclohexylsulfonylamino)-5-trifluoromethylphenoxymethyl] cinnamic acid}$

[0490]

F₃C O COOH

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TLC: Rf 0.27 (AcOEt: hexane = 1:1);

NMR: 8 7.80 (1H, d, J=15Hz), 7.61 (2H, d, J=8Hz), 7.52 (2H, d, J=8Hz), 7.41 (1H, d, J=8Hz), 7.34-7.20 (2H, m), 6.48 (1H, d, J=15Hz), 5.13 (2H, s), 4.32 (1H, m), 2.87 (1H, m), 2.21-2.00 (2H, m), 1.90-1.34 (5H, m), 1.26 (3H, d, J=7Hz), 1.18-0.60 (6H, m).

Reference Example 34

Methyl 4-(3-nitro-5-trifluoromethylpyridine-2-yloxymethyl)benzoate

0 [0491]

F₃C NO₂ COOMe

40

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[0492] To a solution of 2-hydroxy-3-nitro-5-trifluoromethylpyridine (1.0 g) in toluene (10 ml), methyl 4-chloromethylbenzoate (1.32 g) and silver oxide (1.23 g) were added in a stream of argon. The mixture was refluxed for 18 hours with heating. The reaction mixture was filtered. The filtrate was concentrated. The residue was recrystallized from ethyl acetate to give the title compound (982 mg) having the following physical data.

TLC: Rf 0.34 (hexane: AcOEt = 3:1).

50

4-(3-phenylsulfonylamino-5-trifluoromethylpyridine-2-yloxymethyl)benzoic acid

5 **[0493]**

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[0494] By using methyl 4-(3-nitro-5-trifluoromethylpyridine-2-yloxymethyl)benzoate (prepared in Reference Example 34.), the title compound having the following physical data was obtained by the same procedure as Reference Example 12—Reference Example 2.

25

TLC : Rf 0.50 (CHCl₃ : MeOH : AcOH= 100 : 5 : 1); NMR (DMSO- d_6) : δ 12.94 (1H, m), 10.46 (1H, m), 8.33 (1H, m), 7.89 (2H, d, J=8.4Hz), 7.85 (1H, d, J=2.2Hz), 7.73 (2H, m), 7.43-7.65 (3H, m), 7.36 (2H, d, J=8.4Hz), 5.33 (2H, s).

30 Reference Example 35

4-[2-(N-methoxymethyxycarbonylmethyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid • methoxymethyl ester

35 [0495]

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[0496] 4-[2-(N-carboxymethyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid (446 mg) prepared by the same procedure as Example 17—Example 2 by using methyl 4-(2-phenylsulfonylamino-5-trifluoromethylphenoxymethyl)benzoate (prepared in Example 15.) was dissolved in DMF (5 ml). To the solution, methoxymethyl chloride (160 ml) and triethylamine(300 ml) were added dropwise. The mixture was stirred for 2 hours at room temperature. Water was added thereto. The mixture was extracted with ethyl acetate, washed, dried over, filtered and concentrated to give the title compound (476 mg) having the following physical data.

TLC: Rf 0.20 (hexane: AcOEt = 3:1).

Reference Example 36

4-[2-[N-(N,N-dimethylaminocarbonylmethyl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid • methoxymethyl ester

[0497]

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15

F₃C O O OMe

N CONMe₂

O₂S

20

[0498] To a solution of 4-[2-(N-methoxymethoxycarbonylmethyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid • methoxymethyl ester (476 mg; prepared in Reference Example 35.) in THF (2 ml), dimethylamine(0.8 ml) was added. The mixture was stirred for 3 days at room temperature. The solvent was distilled off. The residue was purified on silica gel column chromatography (hexane : AcOEt = 2 : 1 1 : 1) to give the title compound (290 mg) having the following physical data.

30

TLC: Rf 0.26 (hexane: AcOEt = 1:1).

Example 39

4-[2-[N-(N,N-dimethylaminocarbonylmethyl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid

[0499]

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[0500] By using 4-[2-[N-(N,N-dimethylaminocarbonylmethyl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid • methoxymethyl ester (prepared in Reference Example 36.), the title compound having the following physical data was obtained by the same procedure as Reference Example 23.

TLC: Rf 0.24 (AcOEt);

NMR: 88.10-8.06 (2H, m), 7.71-6.64 (3H, m), 7.55-7.47 (1H, m), 7.42-7.10 (6H, m), 4.94 (2H, s), 4.56 (2H, s), 3.04 (3H, s), 2.86 (3H, s).

Reference Example 37

Methyl 4-phenylsulfonylamino-3-methoxybenzoate

[0501]

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MeOOC OMe

20

25

[0502] By using 4-nitro-3-hydroxybenzoic acid, the title compound having the following physical data was obtained by the same procedure as Reference Example 6→Reference Example 12→Reference Example 2.

TLC: Rf 0.12 (hexane: AcOEt = 3:1).

Reference Example 38

1-methyl-1-(4-phenylsulfonylamino-3-methoxyphenyl)ethanol

[0503]

35

OMe NH O₂S

45

40

[0504] To a suspension of methyl 4-phenylsulfonylamino-3-methoxybenzoate (3.2 g; prepared in Reference Example 37.) in THF (50 ml), methyl lithium in ether (38.8 ml) was added dropwise at -65°C. The mixture was slowly warmed to 5°C over a period of 3 hours under stirring. The reaction mixture was neutralized by adding diluted HCl and extracted with ethyl acetate. The organic layer was washed, dried over and concentrated to give the title compound having the following physical data.

TLC: Rf 0.18 (hexane: AcOEt = 1:1).

1-methyl-1-[4-(N-acetyl-phenylsulfonylamino)-3-methoxyphenyi]ethanol

[0505]

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[0506] To a solution of 1-methyl-1-(4-phenylsulfonylamino-3-methoxyphenyl)ethanol (2.65 g; prepared in Reference Example 38.) in methylene chloride (15 ml), acetic anhydride (3.05 ml) and triethylamine (4.60 ml) were added. The mixture was stirred overnight at room temperature. The solvent was distilled off. The residue was purified on silica gel column chromatography (hexane : AcOEt = 3 : 4) to give the title compound (2.33 g) having the following physical data.

25

TLC: Rf 0.19 (hexane: AcOEt = 1:1).

Reference Example 40

2-(N-acetyl-phenylsulfonylamino)-5-isopropylphenyl methyl ether

[0507]

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[0508] To a solution of 1-methyl-1-[4-(N-acetyl-phenylsulfonylamino)-3-methoxyphenyl]ethanol (2.50 g; prepared in Reference Example 39.) in methylene chloride (10 ml), trifluoroacetic acid (10 ml) and triethylsilane (3.3 ml) were added at 0°C. The mixture was stirred for 1 hour at room temperature. The reaction mixture was added to saturated sodium hydrogencarbonate carefully The mixture was extracted with ethyl acetate. The organic layer was washed, dried over and concentrated. The residue was purified on silica gel column chromatography (hexane: AcOEt = 3:1) to give the title compound (2.33 g) having the following physical data. TLC: Rf 0.24 (hexane: AcOEt = 1:1).

2-(N-acetyl-phenylsulfonylamino)-5-isopropylphenol

5 **[0509**]

20

[0510] To a solution of 2-(N-acetyl-phenylsulfonylamino)-5-isopropylphenyl methyl ether (2.28 g; prepared in Reference Example 40.) in methylene chloride (15 ml), boron tribromide (1.36 ml) was added at 0°C. The mixture was stirred for 5 hours at 10°C. The reaction mixture was poured into iced water, extracted with ethyl acetate. The organic layer was washed, dried over and concentrated. The residue was purified on silica gel column chromatography (benzene: AcOEt = 23:2) and recrystallized from AcOEt-hexane mixture solution to give the title compound (1.55 g) having the following physical data.

TLC: Rf 0.24 (benzene: AcOEt = 9:1).

30

Reference Example 42

Methyl 4-[2-(N-acetyl-phenylsulfonylamino)-5-isopropylphenoxymethyl]benzoate

35 [0511]

40 COOMe
O2S

50

[0512] By using 2-(N-acetyl-phenylsulfonylamino)-5-isopropylphenol (1.50 g; prepared in Reference Example 41.), the title compound (2.22 g) having the following physical data was obtained by the same procedure as Reference Example 6.

55

TLC: Rf 0.24 (hexane: AcOEt = 7:3).

4-(phenylsulfonylamino)-3-methoxybenzyl alcohol

[0513]

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[0514] A solution of methyl 4-phenylsulfonylamino-3-methoxybenzoate (1.5 g; prepared in Reference Example 37.) in THF (90 ml) was cooled to -78°C in a stream of argon. The solution of diisobutylaluminum hydride (1.0 M) in hexane (22 ml) was added dropwise thereto. The mixture was stirred for 4 hours at -78°C. After the temperature increased to room temperature, the mixture was diluted with ether (100 ml). A saturated aqueous sodium sulfate (1.5 ml) was added thereto slowly. The mixture was stirred for 30 minutes, dried over, filtered and concentrated to give the title compound (1.5 g)

TLC: Rf 0.31 (AcOEt: hexane = 2:1).

Reference Example 44

4-phenylsulfonylamino-3-methoxybenzaldehyde

[0515]

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[0516] To a solution of 4-phenylsulfonylamino-3-methoxybenzyl alcohol (522 mg; prepared in Reference Example 43.) in methylene chloride (15 ml), manganese dioxide (3 g) was added in a stream of argon. The solution was stirred for 1 hour at room temperature. After the termination of reaction, the reaction mixture was filtered. The filtrate was concentrated to give the title compound (404 mg) having the following physical data.

55 TLC: Rf 0.57 (AcOEt: hexane = 3:2).

1-(4-phenylsulfonylamino-3-methoxyphenyl)ethanol

5 [0517]

OH OME
NH
O2S

20

[0518] A solution of 4-phenylsulfonylamino-3-methoxybenzaldehyde (400 mg; prepared in Reference Example 44.) in THF (10 ml) was cooled to at -78°C mg; prepared in Reference Example 44) in THF (10 ml) was cooled to at -78°C in a stream of argon. A solution of methyl lithium (1.0M) in diethyl ether (3.4 ml) was added dropwise thereto. The mixture was stirred for 20 minutes. After the termination of reaction, a mixture of H₂O + 1N HCl was added thereto to stop the reaction. The mixture was extracted with ethyl acetate three times. The organic layer was washed, dried over and purified on silica gel column chromatography (AcOEt: hexane = 1:1) to give the title compound (421 mg) having the following physical data.

TLC: Rf 0.34 (AcOEt: hexane = 3:2).

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Example 40

4-(2-phenylsulfonylamino-5-isopropylphenoxymethyl)benzoic acid

35 **[0519**]

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[0520] By using methyl 4-[2-(N-acetyl-phenylsulfonylamino)-5-isopropylphenoxymethyl)benzoate (2.00 g; prepared in Reference Example 42.), the title compound (1.66 g) having the following physical data was obtained by the same procedure as Example 2.

55

TLC: Rf 0.49 (CHCl₃: MeOH = 4:1);

NMR (DMSO- d_6): δ 7.84 (2H, d, J=8.5Hz), 7.79-7.53 (5H, m), 7.41 (2H, d, J=8.5Hz), 6.90 (1H, d, J=8Hz), 6.63 (1H, d, J=2Hz), 6.55 (1H, dd, J=8 and 2Hz), 4.82 (2H, s), 2.72 (1H, m), 1.10 (6H, d, J=7Hz).

[0521]

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NH O₂S

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[0522] By using 1-(4-phenylsulfonylamino-3-methoxyphenyl)ethanol (prepared in Reference Example 45.), the title compound having the following physical data was obtained by the same procedure as Reference Example 40 →Reference Example 39→Reference Example 41→Reference Example 6→ Example 2.

TLC: Rf 0.29 (AcOEt: hexane: AcOH= 5:14:1); NMR (DMSO-d₆): δ 12.87 (1H, brs), 9.53 (1H, brs), 7.83 (2H, d, J=8.5Hz), 7.78-7.50 (5H, m), 7.39 (2H, d, J=8.0Hz), 6.86 (2H, d, J=8.0Hz), 6.57 (1H, d, J=2.0Hz), 6.50 (1H, dd, J=8, 2Hz), 4.82 (2H, brs), 2.44 (2H, q, J=7.5Hz), 1.08 (3H, t, J=7.5Hz).

Example 42

4-(2-phenylsulfonylamino-5-hydroxymethylphenoxymethyl)benzoic acid

[0523]

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[0524] By using methyl 4-nitro-3-hydroxybenzoate, the title compound having the following physical data was obtained by the same procedure as Reference Example 19→Reference Example 20→Reference Example 2→Reference Example 43→Reference Example 23→Reference Example 23→Reference Example 2.

TLC: Rf 0.39 (AcOEt: hexane: AcOH= 13:6:1);

NMR (DMSO-d₆): δ 12.83 (1H, brs), 9.56 (1H, s), 7.83 (2H, d, J=8.5Hz), 7.78-7.50 (5H, m), 7.38 (2H, d, J=8.5Hz), 6.88 (1H, d, J=8.0Hz), 6.74 (1H, s), 6.56 (1H, d, J=8.0Hz), 5.10 (1H, brt, J=5.5Hz), 4.83 (2H, s), 4.34 (2H, d, J=5.5Hz).

Reference Example 46

Methyl 4-chloro-2-hydroxybenzoate

[0525]

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[0526] To a solution of 4-chloro-2-hydroxybenzoic acid (5.0 g) in ether (50 ml), diazomethane in ether was added until the reaction was terminated at 0°C. The reaction mixture was concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (hexane: AcOEt = 4:1) to give the title compound (5.4 g) having the 20 following physical data.

TLC: Rf 0.60 (hexane: AcOEt = 2:1).

Reference Example 47

25

2-hydroxymethyl-5-chlorophenol

[0527]

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[0528] To a solution of lithium aluminum hydride (1.1 g) in THF (50 ml),

40 [0529] To a solution of lithium aluminum hydride (1.1 g) in THF (50 ml), methyl 4-chloro-2-hydroxybenzoate (5.38 g;

prepared in Reference Example 46.) in THF (50 ml) was added dropwise in a stream of argon at 0°C. After the solution was warmed to at room temperature, the solution was stirred for 30 minutes. To the reaction mixture, water was added. The mixture was extracted with mixture solution of ether-AcOEt, washed, dried over and concentrated under the reduced pressure. The residue was recrystallized from mixture solution of hexane-AcOEt to give the title compound 45 (3.92 g) having the following physical data.

TLC: Rf 0.60 (hexane: AcOEt = 1:1).

Methyl 4-(2-mesyloxymethyl-5-chlorophenoxymethyl)benzoate

5 [0530]

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[0531] By using 2-hydroxymethyl-5-chlorophenol (prepared in Reference Example 47.), the title compound having the following physical data was obtained by the same procedure as Reference Example 6->Reference Example 8.

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TLC: Rf 0.60 (benzene: acetone = 9:1).

Reference Example 49

25 Methyl 4-(2-azidomethyl-5-chlorophenoxymethyl)benzoate

[0532]

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[0533] To a solution of methyl 4-(2-mesyloxymethyl-5-chlorophenoxymethyl)benzoate (628 mg; prepared in Reference Example 48.) in DMF (5.0 ml), sodium azide (530 mg) was added in a stream of argon. The mixture was stirred for 40 minutes at 60° C. The reaction mixture was diluted with ethyl acetate. The impurity was filtered with celite. The filtrate was washed, dried over and concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (hexane: AcOEt = 10:1) to give the title compound (404 mg) having the following physical data.

TLC: Rf 0.56 (hexane: AcOEt = 4:1).

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Methyl 4-(2-aminomethyl-5-chlorophenoxymethyl)benzoate

[0534]

COOMe

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To a solution of methyl 4-(2-azidomethyl-5-chlorophenoxymethyl)benzoate (389 mg; prepared in Reference Example 49.) in THF (4.0 ml), triphenylphosphine (462 mg) was added at room temperature. The mixture was stirred for 3 hours. After stirring, water was added thereto. The mixture was stirred for 15 hours. The reaction mixture was concentrated under the reduced pressure. The residue was purified on silica gel column chromatography (CHCl₃: MeOH = 50 : 1 10 : 1) to give the title compound (339 mg) having the following physical data.

TLC: Rf 0.22 (CHCi₃: MeOH = 10:1).

Example 43

4-(2-phenylsulfonylaminomethyl-5-chlorophenoxymethyl)benzoic acid

[0536]

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СООН

[0537] By using methyl 4-(2-aminomethyl-5-chlorophenoxymethyl)benzoate (prepared in Reference Example 50.), the title compound having the following physical data was obtained by the same procedure as Reference Example 2→Example 2.

TLC: Rf 0.49 (CHCl3: MeOH: AcOH= 100: 5:1);

NMR (DMSO- d_6): δ 7.94 (2H, d, J=8.0Hz), 7.77 (2H, m), 7.45-7.70 (5H, m), 7.25 (1H, d, J=8.2Hz), 7.05 (1H, d, d, J=8.2Hz), 7.05 (1H, J=1.8Hz), 6.94 (1H, dd, J=1.8, 8.2Hz), 5.20 (2H, s), 4.00 (2H, s).

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 $\hbox{$4$-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl] phenylpropiolic acid}$

[0538]

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[0539] By using 4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid (prepared in Example 18 (9).), the title compound having the following physical data was obtained by the same procedure as Reference Example 13—Reference Example 15—Example 2.

TLC : Rf 0.32 (CHCl₃ : MeOH = 8:2);

NMR : δ 7.80 (2H, d, J=8Hz), 7.64 (2H, d, J=8Hz), 7.68-7.26 (8H, m), 5.09 (2H, s), 4.38 (1H, sept, J=6.5Hz), 1.04 (6H, d,J=6.5Hz).

Example 45

4-[2-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenyl]ethyl]benzoic acid

[0540]

F₃C COOH

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[0541] By using methyl 4-[2-(2-t-butoxycarbonylamino-5-trifluoromethylphenyl)-(EZ)-vinyl]benzoate, the title compound having the following physical data was obtained by the same procedure as Reference Example 20—Reference Example 23—Reference Example 27—Example 2.

TLC: Rf 0.46 (CHCl₃: MeOH = 9:1);

NMR : δ 8.09 (2H, d, J=8.2Hz), 7.8-7.7 (2H, m), 7.7-7.3 (7H. m), 6.88 (1H, d, J=8.2Hz), 4.7-4.5 (1H, m), 3.4-3.1

(2H, m), 3.1-2.9 (2H, m), 1.03 (3H, d, J=6.8Hz), 0.93 (3H, d, J=6.8Hz).

Example 46

4-(2-phenylsulfonylamino-4-chlorophenoxymethyl)benzyl alcohol

[0542]

15 CI NH O2S 20

[0543] By using methyl 4-(2-phenylsulfonylamino-4-chlorophenoxymethyl)benzoate (prepared in Example 7 (a).), the title compound having the following physical data was obtained by the same procedure as Reference Example 43.

TLC: Rf 0.24 (hexane: AcOEt = 1:1); NMR: δ 7.75 (2H, m), 7.60 (1H, d, J=2.4Hz), 7.55 (1H, m), 7.45 (2H, m), 7.36 (2H, d, J=8.0Hz), 7.13 (2H, d, J=8.0Hz), 7.03 (1H, brs), 6.96 (1H, dd, J=2.4, 8.8Hz), 6.68 (1H, d, J=8.8Hz), 4.86 (2H, s), 4.73 (2H, d, J=5.8Hz), 1.74 (1H, t, J=5.8Hz).

Example 47

4-[N-[2-(4-chlorophenylsulfonylamino)-5-chlorophenyl]aminosulfonyl]benzoic acid

[0544]

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[0545] By using 2-nitro-4-chloroaniline, the title compound having the following physical data was obtained by the same procedure as Reference Example 2—Reference Example 12—Reference Example 2.

TLC : Rf 0.22 (CHCl₃ : MeOH : $H_2O = 8 : 2 : 0.2$); NMR (DMSO-d₆) : δ 9.68 (1H, br), 8.11 (2H, d, J=8.4Hz), 7.84 (2H, d, J=8.4Hz), 7.69 (2H, d, J=8.8Hz), 7.62 (2H, d, J=8.4Hz), 7.62 (2H, d, J=8.4Hz)

d, J=8.8Hz), 7.12 (1H, dd, J=2.4 and 8.4Hz), 7.02 (1H, d, J=2.4Hz), 6.97 (1H, d, J=8.4Hz).

Example 48

4-[2-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenyl]-(E)-vinyl]benzoic acid

[0546]

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F₃C COOH

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[0547] By using methyl 4-[2-(2-t-butoxycarbonylamino-5-trifluoromethylphenyl)-(E)-vinyl]benzoate, the title compound having the following physical data was obtained by the same procedure as Reference Example 23→Reference Example 2→Example 17→Example 2.

TLC: Rf 0.45 (CHCl₃: MeOH = 9:1);

NMR : δ 8.2-8.0 (3H, m), 7.9-7.7 (2H, m), 7.6-7.4 (7H, m), 7.2-7.0 (2H, m), 4.8-4.6 (1H, m), 1.08 (3H, d, J=5.0Hz), 1.05 (3H, d, J=5.0Hz).

Example 48(1)

4-[2-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenyl]-(Z)-vinyl]benzoic acid

[0548]

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[0549] By using methyl 4-[2-(2-t-butoxycarbonylamino-5-trifluoromethylphenyl)-(Z)-vinyl]benzoate, the title compound having the following physical data was obtained by the same procedure as Reference Example 23—Reference Example 2-Example 17—Example 2.

55 TLC: Rf 0.51 (CHCl₃: MeOH = 9:1);

NMR : δ 7.97 (2H, d, J=8.4Hz), 7.9-7.7 (2H, m), 7.7-7.4 (5H, m), 7.31 (2H, d, J=8.4Hz), 7.1-6.9 (2H, m), 6.77 (1H, d, J=12.4Hz), 4.7-4.5 (1H, m), 1.19 (3H, d, J=6.6Hz), 1.04 (3H, d, J=6.6Hz).

4-(2-benzoylamino-5-chlorophenoxymethyl)benzoic acid

[0550] 5

COOH

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[0551] By using 2-nitro-5-chlorophenol, the title compound having the following physical data was obtained by the same procedure as Reference Example 6→Reference Example 12→Example 11→ Example 2.

TLC: Rf 0.51 (CHCl3: MeOH: AcOH= 100:5:1);

NMR (DMSO-d₆): 8 12.92 (1H, brs), 9.64 (1H, s), 7.94 (4H, m), 7.75 (1H, d, J=8.6Hz), 7.47-7.68 (5H, m), 7.23 (1H, d, J=2.2Hz), 7.05 (1H, dd, J=2.2, 8.6Hz), 5.32 (2H, s).

Example 50-50(2)

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[0552] By using 4-(2-phenylsulfonylamino-5-isopropylphenoxymethyl)benzoic acid (prepared in Example 40.) or 4-(2phenylsulfonylamino-5-ethylphenoxymethyl)benzoic acid (prepared in Example 41.), the title compounds having the following physical data were obtained by the same procedure as Reference Example 1→Example 1→Example 2.

35 Example 50

4-[2-(N-isopropyl-phenylsulfonylamino)-5-isopropylphenoxymethyl]benzoic acid

[0553]

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COOH

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TLC: Rf 0.13 (CHCl₃: MeOH = 19:1); NMR (DMSO-d₆): δ 7.85 (2H, d, J=8Hz), 7.79-7.52(5H, m), 7.40 (2H, d, J=8Hz), 7.01 (1H, d, J=8Hz), 6.73 (1H, d, J=2Hz), 6.65 (1H, dd, J=8 and 2Hz), 4.83 (2H, brs), 4.47 (1H, m), 2.80 (1H, m), 1.1 4 (6H, d, J=7Hz), 0.95 (6H, d,

J=7Hz).

Example 50(1)

4-[2-(N-methyl-phenylsulfonylamino)-5-isopropylphenoxymethyl]benzoic acid

[0554]

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25 TLC: Rf 0.13 (CHCl₃: MeOH = 19:1);

J=2Hz), 6.70 (1H, dd, J=8 and 2Hz), 4.78 (2H, brs), 3.33 (3H, s), 2.82 (1H, m), 1.15 (6H, d, J=7Hz).

Example 50(2)

4-[2-(N-isopropyl-phenylsulfonylamino)-5-ethylphenoxymethyl]benzoic acid

[0555]

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COOH 40

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50 TLC: Rf 0.40 (AcOEt: hexane: AcOH= 5:14:1);

NMR : δ 7.97 (2H, d, J=8.0Hz), 7.82-7.70 (2H, m), 7.62-7.32 (5H, m), 7.05 (1H, d, J=8.0Hz), 6.60 (1H, dd, J=8, MR) 1.5Hz), 6.53 (1H, d, J=1.5Hz), 4.86 (2H, brs), 4.36 (1H, qn, J=6.0Hz), 2.55 (2H, q, J=7.5Hz), 1.18 (3H, t, J=7.5Hz),

1.02 (6H, brd, J=6.0Hz).

4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid · sodium salt

[0556]

F₃C COONa O₂S

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[0557] To a solution of 4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid (425 mg; prepared in Example 18(40).) in MeOH (5 ml), 2N NaOH (0.41 ml) was added. The mixture was stirred at room temperature. The mixture was distilled off azeotropically with benzene three times to give the title compound (430 mg) having the following physical data.

TLC : Rf 0.19 (hexane : AcOEt = 1 : 1); NMR : δ 7.60 (2H, d, J=7Hz), 7.40-6.97 (11H, m), 6.47 (1H, d, J=16Hz), 4.62 (2H, bs), 4.20-4.08 (1H, m), 0.77 (6H, d, J=5Hz).

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Example 52(1)-52(5)

[0558] By using methyl 4-(2-amino-5-trifluoromethylphenoxymethyl)benzoate (prepared in Reference Example 17.) and the corresponding benzenesulfonylchloride derivatives, the title compounds having the following physical data were obtained by the same procedure as Example 4-Example 19 (isopropanol was used instead of cyclopentylmethanol.)-Example 2.

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Example 52(1)

 $\hbox{$4$-[2-(N-isopropyl-4-propoxyphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]} benzoic acid$

[0559]

F₃C COOH

O₂S OC₃H₇

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TLC: Rf 0.55 (CHCl₃: MeOH = 9:1);

NMR : δ 8.16 (2H, d, J=8.8Hz), 7.71 (2H, d, J=8.8Hz), 7.54 (2H, d, J=8.8HZ), 7.30-7.22 (3H, m), 6.80 (2H, d, J=8.8Hz), 5.14 (2H, s), 4.44-4.24 (1H, m), 3.92 (2H, t, J=6.6Hz), 1.91-1.72 (2H, m), 1.14-0.98 (9H, m).

Example 52(2)

 $\hbox{$4$-[2-(N-isopropyl-4-ethylthiophenylsulfonylamino)-5-trifluoromethylphenoxymethyl]} benzoic\ acid$

[0560]

F₃C O COOH

O₂S SC₂H₅

45

TLC: Rf 0.64 (CHC I_3 : MeOH = 9:1);

NMR: δ 8.17 (2H, d, J=8.4Hz), 7.66 (2H, d, J=8.4Hz), 7.53 (2H, d, J=8.4Hz), .30-7.20 (3H, m), 7.16 (2H, d, J=8.4Hz), 5.12 (2H, s), 4.44-4.22 (1H, m), 2.98 (2H, q, J=7.6Hz), 1.36 (3H, t, J=7.6Hz), 1.09 (3H, d, J=6.6Hz), 1.05 (3H, d, J=6.6Hz).

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Example 52(3)

4-[2-(N-isopropyl-4-methylthiophenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

5 **[0561**]

10 F₃C COOH
O₂S SMe

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TLC: Rf 0.56 (CHCl₃: MeOH = 9:1);

NMR: δ 8.16 (2H, d, J=8.4Hz), 7.67 (2H, d, J=8.4Hz), 7.52 (2H, d, J=8.4Hz), 7.30-7.20 (3H, m), 7.12 (2H, d, J=8.4Hz), 5.12 (2H, s), 4.46-4.24 (1H, m), 2.48 (3H, s), 1.09 (3H, d, J=7.0Hz), 1.05 (3H, d, J=7.0Hz).

Example 52(4)

4-[2-(N-isopropyl-4-butoxyphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

[0562]

F₃C COOH
O₂S OC₄H₉

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TLC: Rf 0.51 (CHCl3: MeOH = 9:1);

NMR: δ 8.16 (2H, d, J=8.4Hz), 7.71 (2H, d, J=8.8Hz), 7.54 (2H, d, J=8.4Hz), 7.30-7.22 (3H, m), 6.79 (2H, d, J=8.8Hz), 5.14 (2H, s), 4.42-4.27 (1H, m), 3.96 (2H, t, J=6.2Hz), 1.87-1.70 (2H, m), 1.60-1.40 (2H, m), 1.14-0.92 (9H, m).

Example 52(5)

 $\hbox{$4$-[2-(N-isopropyl-4-isopropoxyphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]} benzo ic acid$

[0563]

F₃C COOH

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TLC: Rf 0.68 (CHCl3: MeOH = 9:1);

NMR : δ 8.17 (2H, d, J=8.0Hz), 7.71 (2H, d, J=8.8Hz), 7.56 (2H, d, J=8.0Hz), 7.30-7.22 (3H, m), 6.78 (2H, d, J=8.8Hz), 5.15 (2H, s), 4.62-4.50 (1H, m), 4.40-4.23 (1H, m), 1.35 (6H, d, J=5.8Hz), 1.08 (3H, d, J=7.4Hz), 1.04 (3H, d, J=7.4Hz).

Example 53(1)-53(3)

[0564] By using methyl 4-(2-amino-5-chlorophenoxymethyl)benzoate (prepared in Reference Example 7.) or methyl 4-(2-amino-5-trifluoromethyl)benzoate (prepared in Reference Example 17.), the title compounds having the following physical data were obtained by the same procedure as Example 27 (the corresponding aldehyde was used.)—Example 11—Example 2.

Example 53(1)

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4-[2-(N-isobutyl-benzoylamino)-5-chlorophenoxymethyl]benzoic acid

[0565]

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TLC: Rf 0.53 (CHCl₃: MeOH = 5:1); NMR(CDCl₃+1drop of CD₃OD): δ 8.08 (2H, d, J=8Hz), 7.44-7.04 (8H, m), 6.94-6.80 (1H, m), 6.73 (1H, s), 5.03 (1H, d, J=13Hz), 4.82 (1H, d, J=13Hz), 3.91 (1H, dd, J=15, 7Hz), 3.49 (1H, dd, J=15, 7Hz), 2.10-1.60 (1H, m), 0.98 (6H, d, J=7Hz).

Example 53(2)

4-[2-(N-isopropyl-benzoylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

⁵ [0566]

10 F₃C COOH

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TLC : Rf 0.49 (CHCl₃ : MeOH = 9 : 1);

NMR : δ 8.18 (2H, d, J=8.4Hz), 7.52-7.35 (3H, m), 7.30-7.03 (6H, m), 7.02-6.92 (1H, m), 5.20-4.90 (2H, m), 4.90-4.70 (1H, m), 1.50-1.00 (6H, m).

Example 53(3)

4-[2-(N-isopropyl-2-furoylamino)-5-trifluoromethylphenoxymethyl]benzoic acid

30 [0567]

F₃C COOH

45

TLC : Rf 0.43 (CHCl₃ : MeOH = 9 : 1);

NMR: δ 8.09 (2H, d, J=7.8Hz), 7.43-7.22 (5H, m), 7.15 (1H, s), 6.25-6.20 (1H, m), 6.16-6.08 (1H, br), 5.20-4.84 (3H, m), 1.40-1.00 (6H, m).

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4-(2-benzoylamino-5-chlorobenzoylamino)benzoic acid

5 **[0568]**

CI NH COOH

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[0569] By using 2-nitro-5-chlorobenzoic acid chloride (prepared in Reference Example 13.), the title compound having the following physical data was obtained by the same procedure as Example 11→Reference Example 10→Example 11→Example 2.

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TLC : Rf 0.52 (AcOEt : hexane : AcOH= 7 : 12 : 1); NMR (DMSO-d₆) : δ 12.77 (1H, brs), 11.33 (1H, s), 10.85 (1H, s), 8.36 (1H, d, J=9.0Hz), 8.02-7.78 (7H, m), 7.69 (1H, dd, J=9.0, 2.5Hz), 7.64-7.48 (3H, m).

30 Example 55(1)-55(2)

[0570] By using 2-nitro-5-chlorobenzoic acid chloride (prepared in Reference Example 13.), the title compounds having the following physical data were obtained by the same procedure as Examples 11→Reference Example 10→Reference Example 2→Example 2.

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Example 55(1)

4-[2-(2-thienylsulfonylamino)-5-chlorobenzoylamino]benzoic acid

40 [0571]

CI NH O2S S

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TLC : Rf 0.18 (CHCl₃ : MeOH \approx 9 : 1) NMR (DMSO-d₆) : δ 12.73 (1H, br), 10.68 (1H, brs), 10.48 (1H, brs), 7.93 (2H, d, J=8.8Hz), 7.87 (1H, dd, J=1.2 and 3.6Hz), 7.81 (1H, d, J=2.2Hz), 7.76 (2H, d, J=8.8Hz), 7.61-7.53 (2H, m), 7.41 (1H, d, J=8.8Hz), 7.05 (1H, dd, J=3.8Hz), 7.05 (1H, dd,

and 4.0Hz).

Example 55(2)

5 4-(2-butylsulfonylamino-5-chlorobenzoylamino)benzoic acid

[0572]

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TLC: Rf 0.26 (CHCl₃: MeOH = 9:1);

NMR (DMSO-d₆) : δ 12.77 (1H, brs), 10.80 (1H, brs), 9.94 (1H, s), 7.93 (2H, d, J=8.8Hz), 7.88 (1H, d, J=2.2Hz), 7.82 (2H, d, J=8.8Hz), 7.61 (1H, dd, J=2.2 and 8.8Hz), 7.54 (1H, d, J=8.8Hz), 3.18 (2H, t-like), 1.66-1.51 (2H, m), 1.37-1.19 (2H, m), 0.74 (3H, t, J=7.2Hz).

Reference Example 51

Methyl 4-(2-nitro-5-methylphenylthiomethyl)benzoate

[0573]

Me S COOMe

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[0574] To a solution of methyl 4-acetylthiomethylbenzoate (794 mg) in MeOH (5.0 ml), sodium methoxide (191 mg) and 3-fluoro-4-nitrotoluene (500 mg) were added succeedingly in a stream of argon at 0°C. The mixture was warmed slowly to become at room temperature. The mixture was stirred for 4 hours. To the reaction mixture, a saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate, washed, dried over and concentrated under the reduced pressure. The residue was recrystrallized from ethanol to give the title compound (646 mg) having the following physical data.

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TLC: Rf 0.49 (hexane: CH_2CI_2 : AcOEt = 8:4:1).

4-[2-(N-isopropyl-2-furanylsulfonylamino)-5-methylphenylthiomethyl]benzoic acid

[0575]

Me S COOH

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[0576] By using methyl 4-(2-nitro-5-methylphenylthiomethyl)benzoate (prepared in Reference Example 51.), the title compound having the following physical data was obtained by the same procedure as Reference Example 11→Reference Example 2→Example 17→Example 2.

*2*5

TLC : Rf 0.45 (CHCl $_3$: MeOH : AcOH= 100 : 5 : 1); NMR : δ 8.04 (2H, d, J=8.4Hz), 7.58 (1H, dd, J=0.8, 1.8Hz), 7.48 (2H, d, J=8.4Hz), 7.08 (1H, m), 6.91-6.98 (2H, m), 6.84 (1H, d, J=8.0Hz), 6.50 (1H, dd, J=2.0, 3.8Hz), 4.47 (1H, sept, J=6.8Hz), 4.19 (2H, s), 2.28 (3H, s), 1.16 (3H, d, J=6.8Hz), 1.06 (3H, d, J=6.8Hz).

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Example 57

4-[2-(N-isobutyl-2-thienylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

35 [0577]

F₃C COOH

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[0578] By using 2-nitro-5-trifluoromethylphenol, the title compound having the following physical data was obtained by the same procedure as Reference Example 18 (b)→Reference Example 12→Reference Example 2→Example 17→Example 2.

55 TLC: Rf 0.51 (CHCl₃: MeOH: AcOH= 100:5:1);

NMR : δ 7.80 (1H, d, J=16.2Hz), 7.57 (2H, d, J=8.0Hz), 7.22-7.46 (6H, m), 7.16 (1H, m), 6.93 (1H, dd, J=4.0, 5.2Hz), 6.49 (1H, d, J=16.2Hz), 4.94 (2H, brs), 3.45 (2H, d, J=7.2Hz), 1.62 (1H, m), 0.91 (6H, d, J=6.6Hz).

6-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]-2-naphthalic acid

5 [0579]

F₃C COOH

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[0580] By using 2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenol (prepared in Reference Example 24.) and ethyl 6-hydroxymethyl-2-naphthate, the title compound having the following physical data was obtained by the same procedure as Reference Example 18 (b)—Example 2.

25

TLC : Rf 0.55 (CHCl₃ : MeOH : AcOH = 100 : 5 : 1); NMR : δ 8.74 (1H, s), 8.17 (1H, dd, J=1.8, 8.8Hz), 8.03 (1H, d, J=8.4Hz), 8.03 (1H, brs), 7.95 (1H, d, J=8.8Hz), 7.79-7.87 (2H, m), 7.61 (1H, dd, J=1.4, 8.4Hz), 7.43 (1H, m), 7.32 (3H, m), 7.26 (2H, m), 5.26 (2H, s), 4.39 (1H, m), 1.08 (3H, d, J=6.6Hz), 1.06 (3H, d, J=6.6Hz).

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Example 59(1)-59(3)

[0581] By using 2-nitro-5-trifluoromethylphenol, the title compounds having the following physical data were obtained by the same procedure as Reference Example 18 (b)→Reference Example 12→Example 27→Example 11→Example 2.

Example 59(1)

4-[2-(N-isopropyl-2-furoylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

[0582]

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TLC: Rf 0.44 (CHCl₃: MeOH = 9:1);

NMR: δ 7.76 (1H, d, J=16.2Hz), 7.52 (2H, d, J=8.4Hz), 7.38 (1H, d, J=8.4Hz), 7.32 (1H, d, J=8.4Hz), 7.28-7.20 (3H, m), 7.17 (1H, s), 6.45 (1H, d, J=16.2Hz), 6.24-6.19 (1H, m), 6.11-6.00 (1H, br), 5.20-4.80 (3H, m), 1.40-1.00 (6H, m).

5 Example 59(2)

4-[2-(N-isobutyl-2-furoylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

[0583]

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F₃C COOH

25 TLC: Rf 0.49 (CHCl₃: MeOH = 9:1);

NMR : δ 7.76 (1H, d, J=15.9Hz), 7.52 (2H, d, J=8.4Hz), 7.39 (1H, d, J=8.1Hz), 7.33-7.15 (5H, m), 6.45 (1H, d, J=15.9Hz), 6.28-6.10 (2H, m), 5.20-4.90 (2H, m), 4.00-3.80 (1H, br), 3.60-3.30 (1H, br), 2.00-1.80 (1H, m), 0.95 (6H, d, J=6.6Hz).

30 Example 59(3)

4-[2-(N-isopropyl-butyrylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

[0584]

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TLC: Rf 0.42 (CHCl3: MeOH = 9:1);

NMR: δ 7.78 (1H, d, J=15.9Hz), 7.58 (2H, d, J=8.1Hz), 7.42 (2H, d, J=8.1Hz), 7.35-7.20 (3H, m), 6.48 (1H, d, J=15.9Hz), 5.20-4.93 (3H, m), 1.90 (2H, dt, J=2.7, 7.5Hz), 1.64-1.50 (2H, m), 1.17 (3H, d, J=6.6Hz), 0.94 (3H, d, J=6.6Hz),

0.79 (3H, t, J=7.2Hz).

Example 60(1)-60(2)

[0585] By using 2-nitro-5-trifluoromethylphenol, the title compounds having the following physical data were obtained

by the same procedure as Reference Example 18 (b)→Reference Example 12→Reference Example 2→Example 19→Example 2.

Example 60(1)

 $\hbox{$4$-[2-(N-isopropyl-4-ethoxyphenylsulfonylamino)-5-trifluoromethylphenoxymethyl] cinnamic acid}$

[0586]

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F₃C OOH
O₂S OC₂H₅

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25 TLC: Rf 0.51 (CHCl₃: MeOH = 9:1);

NMR: δ 7.82 (1H, d, J=16.0Hz), 7.72 (2H, d, J=8.8Hz), 7.61 (2H, d, J=8.6Hz), 7.48 (2H, d, J=8.6Hz), 7.28-7.22 (3H, m), 6.77 (2H, d, J=8.8Hz), 6.50 (1H, d, J=16.0Hz), 5.10 (2H, s), 4.40-4.20 (1H, m), 4.01 (2H, q, J=6.8Hz), 1.43 (3H, t, J=6.8Hz), 1.07 (3H, d, J=6.6Hz), 1.03 (3H, d, J=6.6Hz).

30 <u>Example 60(2)</u>

4-[2-(N-isobutyl-4-ethoxyphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid

[0587]

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TLC: Rf 0.57 (CHCl₃: MeOH = 9:1);

NMR: δ 7.81(1H, d, J=15.6Hz), 7.60-7.47 (3H, m), 7.44 (1H, d, J=8.2Hz), 7.30-7.10 (5H, m), 6.73(2H, d, J=8.8Hz), 6.50 (1H, d, J=15.6Hz), 5.00-4.80 (2H, br), 3.95 (2H, q, J=7.0Hz), 3.39 (2H, d, J=6.8Hz), 1.70-1.50 (1H, m), 1.41 (3H, t, J=6.8Hz), 0.88 (6H, d, J=6.6Hz).

Example 61

 $\hbox{$4$-[2-(N-isopropyl-3-ethoxyphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]} benzoic\ acid$

5 **[0588]**

F₃C OC₂H₅

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[0589] By using methyl 4-(2-amino-5-trifluoromethylphenoxymethyl)benzoate (prepared in Reference Example 17.), the title compound having the following physical data was obtained by the same procedure as Example 4->Example 19->Example 2.

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TLC : Rf 0.63 (CHCl $_3$: MeOH = 9 : 1); NMR : δ 8.15 (2H, d, J=8.4Hz), 7.53 (2H, d, J=8.4Hz), 7.40-7.20 (6H, m), 7.02 (1H, ddd, J=1.2, 2.4, 8.0Hz), 5.13 (2H, s), 4.52-4.36 (1H, m), 3.98 (2H, q, J=6.8Hz), 1.40 (3H, t, J=6.8Hz), 1.08 (3H, d, J=6.6Hz), 1.06 (3H, d, J=6.6Hz).

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Example 62(1)-62(2)

[0590] By using 2-nitrobenzoic acid chloride, the title compounds having the following physical data were obtained by the same procedure as Example 11 \rightarrow Reference Example 20 \rightarrow Reference Example 2 \rightarrow Example 2.

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Example 62(1)

4-[2-(3-chlorophenylsulfonylamino)benzoylamino]benzoic acid

40 [0591]

NH O2S CI

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TLC : Rf 0.38 (CHCl₃: MeOH = 9 : 1); NMR (DMSO-d₆) : δ 10.59 (1H, s), 10.44 (1H, s), 7.95 (2H, d, J=8.4Hz), 7.86-7.60 (6H, m), 7.58-7.45 (2H, m), 7.38-7.45 (2

7.25 (2H, m).

Example 62(2)

5 4-[2-(4-bromophenylsulfonylamino)benzoylamino]benzoic acid

[0592]

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TLC: Rf 0.39 (CHCl₃: MeOH = 9:1);

NMR (DMSO-d₆): δ 10.55 (1H, s), 10.38 (1H, s), 7.96 (2H, d, J=8.8Hz), 7.90-7.45 (8H, m), 7.44-7.25 (2H, m).

Formulation example 1

[0593] The following compounds were admixed in conventional method and punched out to obtain 100 tablets each containing 5 mg of active ingredient.

- 4-(2-phenylsulfonylamino-5-chlorobenzoylamino)benzoic acid (prepared in Example 2.)
 - Cellulose calcium glycolate (disintegrating agent)
 - Magnesium stearate (lubricating agent)
 - Micro crystalline cellulose
 - 4-(2-phenylsulfonylamino-5-chlorobenzoylamino)benzoic acid (prepared in Example 2.)
 - 500 mg
 - 200 mg
 - 100 mg
 - 100 mg
 - 9.2 g

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Claims

1. A sulfonamide or carboamide derivative of the formula (I)

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$$(R^{3})n - B = Z^{3} - N - Z^{4} - Z^{5}$$
(I)

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(wherein

5 and 10 each, independently, is C5-15 carbocyclic ring or 5-7 membered heterocyclic ring containing one or two oxygen, sulfur or nitrogen atom(s), 15 Z¹ is -COR1. -C1-4 alkylene-COR1, 20 -CH=CH-COR1, -C=COR1, or -O-C1-3 alkylene-COR1, (wherein, R1 is hydroxy, C1-4 alkoxy or formula 25 NR6R7 (wherein, R⁶ and R⁷ each, independently, is H or C1-4 alkyl.).), or -C1-5 alkylene-OH, 30 Z² is H, C1-4 alkyl, C1-4 alkoxy, nitro, halogen, trifluoromethyl, trifluoromethoxy, hydroxy or COR¹ (wherein R¹ is as defined hereinbefore.), Z³ is single bond or C1-4 alkylene. Z4 is SO2 or CO, Z⁵ is 35 (1) C1-8 alkyl, C2-8 alkenyl, or C2-8 alkynyl, (2) phenyl, C3-7 cycloalkyl, or 5-7 membered heterocyclic ring containing one or two oxygen, sulfur or nitrogen atom(s), or (3) C1-4 alkyl, C2-4 alkenyl or C2-4 alkynyl substituted by phenyl or C3-7 cycloalkyl 40 (phenyl, C3-7 cycloalkyl and 5-7 membered heterocyclic ring containing one or two oxygen, sulfur or nitrogen atom(s) mentioned in the above (2) and (3) may be substituted by 1-5 of R5 (wherein R5 (if two or more R5, each independently) is H, C1-6 alkyl, C1-6 alkoxy, C1-6 alkylthio, nitro, halogen, tifluoromethyl, trifluoromethoxy or hydroxy.).), 45 R² is

CONR⁸,
NR⁸CO,
CONR⁸-C1-4 alkylene,
C1-4 alkylene-CONR⁸,
NR⁸CO-C1-4 alkylene,
C1-4 alkylene-NR⁸CO,
C1-3 alkylene-CONR⁹-C1-3 alkylene, or
C1-3 alkylene-NR⁸CO-C1-3 alkylene
(wherein each R⁸ is H or C1-4 alkyl.),
O, S, NZ⁶
(wherein Z⁶ is H or C1-4 alkyl.),

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	Z ⁷ -C1-4 alkylene,
	C1-4 alkylene-Z ⁷ , or
	C1-3 alkylene-Z ⁷ -C1-3 alkylene
	(wherein each Z^7 is O, S or NZ^6 (wherein Z^6 is as defined hereinbefore.).)
5	CO,
	CO-C1-4 alkylene,
	C1-4 alkylene-CO,
	C1-3 alkylene-CO-C1-3 alkylene,
	C2-4 alkylene,
10	C2-4 alkenylene, or
	C2-4 alkynylene,
	R3 is H, C1-6 alkyl, C1-6 alkoxy, C1-6 alkylthio, nitro, halogen, trifluoromethyl, trifluoromethoxy, hydroxy or
	hydroxymethyl,
15	R ⁴ is
	(1) H,
	(2) C1-8 alkyl, C2-8 alkenyl, or C2-8 alkynyl,
20	(3) C1-6 alkyl substituted by one or two substituent(s) selected from the group consisting of COOZ ⁸ , CONZ ⁹ Z ¹⁰ , and OZ ⁸ (wherein Z ⁸ , Z ⁹ and Z ¹⁰ each, independently, is H or C1-4 alkyl.) and C1-4 alkoxy-
	C1-4 alkoxy,
	(4) C3-7 cycloalkyl, or
	(5) C1-4 alkyl, C2-4 alkenyl or C2-4 alkynyl substituted by phenyl or C3-7 cycloalkyl
25	(phenyl and C3-7 cycloalkyl mentioned in the above (4) and (5) may be substituted by 1-5 of R5 (wherein R5 is
	as defined hereinbefore.).), and n and t each, independently, is an integer of 1-4.
	with the proviso that (1) R ² and Z ³ should be connected at the 1- or 2- position of
	_
30	
-	(B)
	, and (2) when
35	
	(_A)
40	
	is a benzene ring and (Z ²)t is other than COR ¹ , Z ¹ should be connected at the 3- or 4-position of the benzene
	ring.), or a non-toxic salt thereof.
	2. A compound according to claim 1, wherein
45	and the second s
	(*)
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	and
	(B
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is C5-15 carbocyclic ring and Z^5 is C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, or group containing phenyl or C3-7

cycloalkyl. 3. A compound according to claim 1, wherein at least one of 5 and Z^5 is 5-7 membered heterocyclic ring containing one or two oxygen, sulfur or nitrogen atom(s). 10 A compound according to claim 1 or 3, wherein 15 and 20 is C5-15 carbocyclic ring and Z^5 is 5-7 membered heterocyclic ring containing one or two oxygen, sulfur or nitrogen 25 atom(s). A compound according to claim 1 or 3, wherein one of 30 35 and 40 is 5-7 membered heterocyclic ring containing one or two oxygen, sulfur or nitrogen atom(s) and the other is C5-15 carbocyclic ring. 45 A compound according to claim 1, 2 or 3, wherein R² is CONR8-C1-4 alkylene, C1-4 alkylene-CONR8, 50 C1-3 alkylene-CONR8-C1-3 alkylene, NR8CO, NR8CO-C1-4 alkylene, C1-4 alkylene-NR8CO or 55 C1-3 alkylene-NR8CO-C1-3 alkylene

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(wherein each R8 is H or C1-4 alkyl.).

7. A compound according to claim 1, 2 or 3, wherein R² is

```
O. S. NZ6
              (wherein Z6 is H or C1-4 alkyl.),
              Z7-C1-4 alkylene,
              C1-4 alkylene-Z7, or
 5
              C1-3 alkylene-Z7-C1-3 alkylene
              (wherein each Z^7 is O, S or NZ^6 (wherein Z^6 is as defined hereinbefore.).).
     8. A compound according to claim 1, 2 or 3, wherein R<sup>2</sup> is
 10
              C2-4 alkylene, C2-4 alkenylene or C2-4 alkynylene.
        A compound according to claim 1, 2 or 3, wherein R<sup>2</sup> is
              CO.
             CO-C1-4 alkylene,
 15
             C1-4 alkylene-CO or
             C1-3 alkylene-CO-C1-3 alkylene.
     10. A compound according to claim 1 which is selected from
20
             (1) 4-(2-phenylsulfonylamino-5-chlorobenzoylamino)benzoic acid,
             (2) 3-(2-phenylsulfonylaminobenzoylamino)benzoic acid.
             (3) 3-(2-phenylsulfonylamino-5-chlorobenzoylamino)benzoic acid.
             (4) 4-(2-phenylsulfonylaminobenzoylamino)benzoic acid,
             (5) 4-[2-(4-chlorophenyl)sulfonylamino-5-chlorobenzoylamino]benzoic acid,
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             (6) 4-[2-(4-chlorophenylsulfonylamino)-4-chlorobenzoylamino]benzoic acid,
             (7) 4-[2-(4-chlorophenylsulfonylamino)-6-chlorobenzoylamino]benzoic acid,
             (8) 4-[2-(4-chlorophenylsulfonylamino)-3-chlorobenzoylamino]benzoic acid,
             (9) 4-[2-(2-chlorophenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid.
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             (10) 4-[2-(3-chlorophenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid,
             (11) 4-[2-(4-chlorophenylsulfonylamino)-5-fluorobenzoylamino]benzoic acid,
             (12) 4-[2-(4-chlorophenylsulfonylamino)-5-bromobenzoylamino]benzoic acid,
             (13) 4-[2-(4-chlorophenylsulfonylamino)-5-methoxybenzoylamino]benzoic acid,
             (14) 4-[2-(4-bromophenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid,
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             (15) 4-[2-(4-methylphenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid,
             (16) 4-[2-(4-methoxyphenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid.
             (17) 4-[2-(4-nitrophenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid.
             (18) 4-[2-(2,4-dichlorophenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid.
             (19) 4-[2-(4-n-butylphenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid,
40
             (20) 4-[2-(4-chlorophenylsulfonylamino)benzoylamino]benzoic acid.
             (21) 4-(2-phenylsulfonylamino-5-fluorobenzoylamino)benzoic acid,
             (22) 4-(2-phenylsulfonylamino-4-fluorobenzoylamino)benzoic acid,
             (23) 4-[2-(4-chlorophenylsulfonylamino)-4-fluorobenzoylamino]benzoic acid,
             (24) 4-[2-(4-fluorophenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid.
45
             (25) 4-[2-(4-trifluoromethylphenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid,
             (26) 4-(2-phenylsulfonylamino-5-chlorobenzoylaminomethyl)benzoic acid,
             (27) 4-[2-(2-phenylvinyl)sulfonylamino-5-chlorobenzoylamino]benzoic acid,
             (28) 4-[2-(2-phenylethyl)sulfonylamino-5-chlorobenzoylamino]benzoic acid,
             (29) 4-[2-(4-chlorophenylsulfonylamino)-5-nitrobenzoylamino]benzoic acid,
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             (30) 4-[2-(4-hydroxyphenylsulfonylamino)-5-chlorobenzoylamino]benzoic acid,
             (31) 4-(2-phenylsulfonylamino-5-chlorophenylaminocarbonyl)benzoic acid.
             (32) 4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylbenzoylamino]benzoic acid,
             (33) 4-[N-[2-(4-chlorophenylsulfonylamino)-5-chlorophenyl]aminosulfonyl]benzoic acid,
             (34) 4-(2-benzoylamino-5-chlorobenzoylamino)benzoic acid.
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             (35) 4-(2-butylsulfonylamino-5-chlorobenzoylamino)benzoic acid,
             (36) 4-[2-(3-chlorophenylsulfonylamino)benzoylamino]benzoic acid and
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(37) 4-[2-(4-bromophenylsulfonylamino)benzoylamino]benzoic acid, and methyl esters thereof.

11. A compound according to claim 1 which is selected from

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(1) 4-[2-(4-chlorophenylsulfonylamino)-5-chlorophenoxymethyl]benzoic acid,
                   (2) 4-(2-phenylsulfonylamino-5-chlorophenoxymethyl)benzoic acid,
                   (3) 4-(2-phenylsulfonylamino-4-chlorophenoxymethyl)benzoic acid.
 5
                   (4) 4-[2-(4-chlorophenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid.
                   (5) 4-[2-(4-chlorophenylsulfonylamino)-5-chlorophenylmethoxy]benzoic acid,
                   (6) 4-(2-phenylsulfonylamino-5-trifluoromethylphenoxymethyl)benzoic acid,
                   (7) 4-[2-(N-isopropyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid,
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                   (8) 4-[2-(N-carboxymethyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid,
                   (9) 4-[2-[N-(2-hydroxyethyl)-phenylsulfonylamino]-4-chlorophenoxymethyl]benzoic acid,
                   (10) 4-[2-(N-methyl-phenylsulfonylamino)-4-trifluoromethylphenoxymethyl]benzoic acid.
                   (11) 4-[2-[N-(2-hydroxyethyl)-phenylsulfonylamino]-4-trifluoromethylphenoxymethyl]benzoic acid,
                   (12) 4-[2-[N-(2-hydroxyethyl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid,
                   (13) 4-[2-(N-methyl-phenylsulfonylamino)-5-chlorophenoxymethyl]benzoic acid,
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                   (14) 4-[2-[N-(2-hydroxyethyl)-phenylsulfonylamino]-5-chlorophenoxymethyl]benzoic acid,
                   (15) 4-[2-(N-methyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
                   (16) 4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
                   (17) 4-[2-(N-isopropyl-phenylsulfonylamino)-5-chlorophenoxymethyl]benzoic acid.
                   (18) 4-[2-(N-isopropyl-phenylsulfonylamino)-4-trifluoromethylphenoxymethyl]benzoic acid.
20
                   (19) 4-[2-[N-(2-methoxyethoxymethyl)-phenylsulfonylamino]-4-chlorophenoxymethyl]benzoic acid,
                   (20) 4-[2-[N-(2-methoxyethyl)-phenylsulfonylamino]-4-chlorophenoxymethyl]benzoic acid,
                   (21) 4-[2-[N-[2-(2-methoxyethoxy)ethyl]-phenylsulfonylamino]-4-chlorophenoxymethyl]benzoic acid,
                   (22) 4-[2-(N-ethyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid,
25
                   (23) 4-(2-(N-propyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid,
                   (24) 4-[2-(N-butyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid,
                   (25) 4-[2-(N-pentyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid.
                   (26) 4-[2-(N-hexyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid.
                   (27) 4-[2-(N-benzyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid,
                   (28) 4-[2-(N-isopropyl-phenylsulfonylamino)-5-methylphenoxymethyl]benzoic acid,
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                   (29) 4-[2-(N-methyl-phenylsulfonylamino)-5-methylphenoxymethyl]benzoic acid,
                   (30) 4-[2-[N-(2-hydroxyethyl)-phenylsulfonylamino]-5-methylphenoxymethyl]benzoic acid,
                   (31) 4-[2-[N-(prop-2-enyl)-phenylsulfonylamino]-4-chlorophenoxymethyl]benzoic acid,
                   (32) 4-[2-(N-cyclopentyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid,
                   (33) 4-[2-[N-(2-methoxyethyl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid,
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                  (34) 4-[2-(N-ethyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid.
                  (35) 4-[2-(N-propyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
                  (36) 4-[2-(N-isobutyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
                  (37) 4-[2-(N-cyclopentyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
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                  (38) 4-[2-[N-(prop-2-enyl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid,
                  (39) 4-[2-[N-(2-methylprop-2-enyl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid,
                  (40) 4-[2-(N-isopropyl-4-methylphenylsulfonylamino)-5-trifluoromethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylphenoxymethylp
                  (41) 4-[2-(N-isopropyl-4-fluorophenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
                  (42) 4-[2-(N-isopropyl-4-methoxyphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
                  (43) 4-[2-(N-isopropyl-phenylsulfonylamino)-5-chlorophenoxy]benzoic acid,
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                  (44) 3-[2-(N-isopropyl-phenylsulfonylamino)-5-chlorophenoxy]cinnamic acid,
                  (45) trans-4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]cyclohexanoic acid,
                  (46) 4-[2-(N-isopropyl-phenylsulfonylamino)-5-chlorophenoxy]phenylacetic acid,
                  (47) 4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl)cinnamic acid,
                  (48) 3-[4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]phenyl]propionic acid,
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                  (49) 3-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]phenylacetic acid,
                  (50) 4-[2-(N-isopropyl-4-ethoxyphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
                  (51) 4-[2-(N-isobutyl-phenylsulfonylamino)-5-methylphenoxymethyl]benzoic acid,
                  (52) 4-[2-(N-isopropyl-phenylsulfonylamino)-5-fluorophenoxymethyf]benzoic acid,
                  (53) 4-[2-(N-isopropyl-phenylsulfonylamino)-5-methoxyphenoxymethyl]benzoic acid,
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                  (54) 4-[2-(N-propyl-phenylsulfonylamino)-5-methylphenoxymethyl]benzoic acid,
                  (55) 4-[2-[N-(prop-2-enyl)-phenylsulfonylamin ]-5-methylphenoxymethyl]benzoic acid.
                  (56) 4-[2-[N-(2-methylprop-2-enyl)-phenylsulfonylamino]-5-methylphenoxymethyl]benzoic acid,
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(57) 4-[2-(N-cyclopropylmethyl-phenylsulfonylamino)-5-methylphenoxymethyl]benzoic acid,
              (58) 4-[2-(N-propyl-phenylsulfonylamino)-5-chlorophenoxymethylibenzoic acid.
              (59) 4-[2-(N-isobutyl-phenylsulfonylamino)-5-chlorophenoxymethylibenzoic acid.
              (60) 4-[2-[N-(prop-2-enyl)-phenylsulfonylamino]-5-chlorophenoxymethyl]benzoic acid,
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              (61) 4-[2-[N-(2-methylprop-2-enyl)-phenylsulfonylamino]-5-chlorophenoxymethyl]benzoic acid,
              (62) 4-[2-(N-cyclopropylmethyl-phenylsulfonylamino)-5-chlorophenoxymethyl]benzoic acid,
              (63) 4-[2-(N-methoxymethyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyllbenzoic acid.
              (64) 4-[2-(N-isobutyl-phenylsulfonylamino)-4-methylphenoxymethyllbenzoic acid.
             (65) 4-[2-(N-isopropyl-phenylsulfonylamino)-4-methylphenoxymethyl]benzoic acid.
             (66) 4-[2-[N-(prop-2-enyl)-phenylsulfonylamino]-4-methylphenoxymethyl]benzoic acid,
 10
             (67) 4-[2-(N-isopropyl-4-ethoxyphenylsulfonylamino)-5-chlorophenoxymethyl]benzoic acid,
             (68) 4-[2-(N-isopropyl-4-ethoxyphenylsulfonylamino)-5-methylphenoxymethyl]benzoic acid,
             (69) 4-[2-(N-ethyl-phenylsulfonylamino)-4-methylphenoxymethyl]benzoic acid,
             (70) 4-[2-(N-propyl-phenylsulfonylamino)-4-methylphenoxymethyllbenzoic acid.
15
             (71) 4-[2-(N-butyl-phenylsulfonylamino)-4-methylphenoxymethyl]benzoic acid.
             (72) 4-[2-[N-(2-methylprop-2-enyl)-phenylsulfonylamino]-4-methylphenoxymethyl]benzoic acid,
             (73) 4-[2-(N-cyclopropylmethyl-phenylsulfonylamino)-4-methylphenoxymethyl]benzoic acid,
             (74) 4-[2-(N-isopropyl-propylsulfonylamino)-5-methylphenoxymethyl]benzoic acid,
             (75) 4-[2-(N-isopropyl-pentylsulfonylamino)-5-methylphenoxymethyl]benzoic acid,
             (76) 4-[2-(N-benzyl-methylsulfonylamino)-5-methylphenoxymethyl]benzoic acid.
20
             (77) 4-[2-(N-benzyl-propylsulfonylamino)-5-methylphenoxymethyl]benzoic acid,
             (78) 4-[2-(N-isopropyl-cyclopentylsulfonylamino)-5-methylphenoxymethyl]benzoic acid.
             (79) 4-[2-(N-isobutyl-ethylsulfonylamino)-4-methylphenoxymethyllbenzoic acid.
             (80) 4-[2-(N-isobutyl-propylsulfonylamino)-4-methylphenoxymethyl]benzoic acid.
25
             (81) 4-[2-(N-isobutyl-butylsulfonylamino)-4-methylphenoxymethyl]benzoic acid,
             (82) 4-[2-(N-isobutyl-propylsulfonylamino)-5-methylphenoxymethyl]benzoic acid,
             (83) 4-[2-[N-(prop-2-enyl)-propylsulfonylamino]-5-methylphenoxymethyl]benzoic acid,
             (84) 4-[2-[N-(2-methylprop-2-enyl)-propylsulfonylamino]-5-methylphenoxymethyl]benzoic acid,
             (85) 4-[2-(N-isobutyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid.
30
             (86) 4-[2-(N-propyl-propylsulfonylamino)-5-methylphenoxymethyl]benzoic acid.
             (87) 4-[2-(N-isobutyl-hexylsulfonylamino)-4-methylphenoxymethyllbenzoic acid.
             (88) 4-[2-(N-isobutyl-pentylsulfonylamino)-4-methylphenoxymethyl]benzoic acid.
             (89) 4-[2-[N-(prop-2-enyl)-propylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid,
             (90) 4-[2-[N-(2-methylprop-2-enyl)-propylsulfonylamino]-5-trifluoromethylphenoxymethylphenoxic acid,
35
             (91) 4-[2-(N-propyl-propylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid.
             (92) 4-[2-(N-isobutyl-propylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
             (93) 4-[2-(N-propyl-phenylsulfonylamino)-5-methylphenoxymethyl]cinnamic acid,
             (94) 4-[2-(N-isobutyl-phenylsulfonylamino)-5-methylphenoxymethyllcinnamic acid.
             (95) 4-[2-(N-isobutyl-propylsulfonylamino)-5-trifluoromethylphenoxymethyllcinnamic acid.
             (96) 4-[2-(N-methyl-phenysulphonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid,
40
             (97) 4-[2-(N-propyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid,
             (98) 4-[2-(N-isobutyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid,
             (99) 4-[2-(N-isopropyl-propylsulfonylamino)-5-methylphenoxymethyl]cinnamic acid,
             (100) 4-[2-(N-ethyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid,
45
             (101) 4-[2-(N-cyclopropylmethyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyllcinnamic acid.
             (102) 4-[2-(N-isopropyl-methylsulfonylamino)-5-trifluoromethylphenoxymethyllcinnamic acid.
             (103) 4-[2-(N-benzyl-propylsulfonylamino)-5-trifluoromethylphenoxy-ethyl]cinnamic acid.
             (104) 4-[2-(N-propyl-phenylsulfonylamino)-4-methylphenoxymethyl]cinnamic acid,
             (105) 4-[2-[N-(prop-2-enyl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]cinnamic acid,
             (106) 4-[2-[N-(2-methylprop-2-enyl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]cinnamic acid,
50
             (107) 4-[2-(N-isobutyl-phenylsulfonylamino)-4-methylphenoxymethyl]cinnamic acid,
             (108) 4-[2-(N-benzyl-methylsulfonylamino)-5-trifluoromethylphenoxymethyllcinnamic acid.
             (109) 4-[2-(N-isopropyl-phenylsulfonylamino)-4-trifluoromethylphenoxymethyllcinnamic acid.
             (110) 4-[2-(N-isobutyl-4-ethoxyphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
             (111) 4-[2-(N-methyl-phenylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid,
55
             (112) 4-[2-(N-cyclopentylmethyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethylibenzoic acid,
             (113) 4-[2-(N-cyclopropylmethyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethylibenzoic acid.
             (114) 4-[2-(N-t-butylmethyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyllbenzoic acid.
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(115) 4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]phenylacetic acid,
             (116) 4-[2-(N-isopropyl-propylsulfonylamino)-5-trifluoromethylphenoxymethylibenzoic acid.
             (117) 4-[2-(N-isopropyl-pentylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
             (118) 4-[2-(N-isopropyl-butylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
5
             (119) 4-[2-(N-isopropyl-hexylsulfonylamino)-5-trifluoromethylphenoxymethyllbenzoic acid.
             (120) 4-[2-(N-isopropyl-heptylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
             (121) 4-[2-(N-isopropyl-4-hydroxyphenylsulfonylamino)-5-trifluoromethylphenoxymethylbenzoic acid.
             (122) 4-[2-(N-isopropyl-butylsulfonylamino)-5-methylphenoxymethylphenzoic acid.
             (123) 4-[2-(N-isopropyl-hexylsulfonylamino)-5-methylphenoxymethyl]benzoic acid,
             (124) 4-[2-(N-isopropyl-heptylsulfonylamino)-5-methylphenoxymethyl]benzoic acid,
10
             (125) 4-[2-(N-isopropyl-methylsulfonylamino)-5-methylphenoxymethyl]benzoic acid.
             (126) 4-[2-(N-isopropyl-ethylsulfonylamino)-5-methylphenoxymethyl]benzoic acid,
             (127) 4-[2-(N-isopropyl-2-phenylethylsulfonylamino)-5-methylphenoxymethyl]benzoic acid,
             (128) 4-[2-(N-isopropyl-benzylsulfonylamino)-5-methylphenoxymethylphenzoic acid.
             (129) 4-[2-(N-t-butylmethyl-phenylsulfonylamino)-4-methylphenoxymethyl]benzoic acid,
15
             (130) 4-[2-(N-isopropyl-methylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
             (131) 4-[2-(N-isopropyl-ethylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
             (132) 4-[2-(N-isopropyl-cyclopentylmethylsulfonylamino)-5-methylphenoxymethylibenzoic acid.
             (133) 4-[2-(N-cyclohexylmethyl-propylsulfonylamino)-5-methylphenoxymethyl]benzoic acid,
             (134) 4-[2-(N-cyclopentylmethyl-propylsulfonylamino)-5-methylphenoxymethyl]benzoic acid,
20
             (135) 4-[2-(N-isopropyl-propylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid.
             (136) 4-[2-(N-isopropyl-pentylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid,
             (137) 4-[2-(N-isopropyl-4-chlorophenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
             (138) 4-[2-(N-isopropyl-4-ethylphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
             (139) 4-[2-(N-isopropyl-4-propylphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
25
             (140) 4-[2-(N-isopropyl-4-butylphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
             (141) 4-(2-phenylsulfonylaminophenoxymethyl)benzoic acid,
             (142) 4-[2-(4-chlorophenylsulfonylamino)phenoxymethyl]benzoic acid,
             (143) 4-(2-phenylsulfonylamino-4-fluorophenoxymethyl)benzoic acid.
30
             (144) 4-(2-phenylsulfonylamino-5-fluorophenoxymethyl)benzoic acid.
             (145) 4-(2-phenylsulfonylamino-4-bromophenoxymethyl)benzoic acid.
             (146) 4-(2-phenylsulfonylamino-5-chlorophenylthiomethyl)benzoic acid,
             (147) 4-(2-phenylsulfonylamino-4-methoxyphenoxymethyl)benzoic acid,
             (148) 4-(2-phenylsulfonylamino-4-trifluoromethylphenoxymethyl)benzoic acid,
35
             (149) 4-(2-phenylsulfonylamino-4-methylphenoxymethyl)benzoic acid.
             (150) 4-(2-phenylsulfonylamino-5-methylphenoxymethyl)benzoic acid,
             (151) 4-(2-benzylsulfonylamino-5-chlorophenoxymethyl)benzoic acid.
             (152) 4-(2-phenylsulfonylamino-5-methoxyphenoxymethyl)benzoic acid.
             (153) 3-(2-phenylsulfonylamino-5-chlorophenoxymethyl)benzoic acid.
             (154) 4-(2-phenylsulfonylamino-4-chloro-5-methylphenoxymethyl)benzoic acid,
40
             (155) 4-(2-phenylsulfonylamino-4,5-dichlorophenoxymethyl)benzoic acid,
             (156) 4-(2-phenylsulfonylamino-5-chlorophenoxymethyl)phthalic acid,
             (157) 4-(2-phenylsulfonylamino-5-chlorophenoxy)benzoic acid.
             (158) 4-[3-(2-phenylsulfonylamino-5-chlorophenoxy)propyl]benzoic acid,
45
             (159) trans-4-(2-phenylsulfonylamino-5-chlorophenoxymethyl)cyclohexanoic acid.
             (160) cis-4-(2-phenylsulfonylamino-5-chlorophenoxymethyl)cyclohexanoic acid.
             (161) 4-[1RS-(2-phenylsulfonylamino-5-chlorophenoxy)ethyl]benzoic acid,
             (162) 4-[2-[N-(2-hydroxy-2-methylpropyl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid,
             (163) 4-[2-[N-(2-hydroxy-2-methylpropyl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]cinnamic acid,
             (164) 4-[2-[N-(2-hydroxy-2-methylpropyl)-phenylsulfonylamino]-5-methylphenoxymethyl]benzoic acid,
50
             (165) 4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyllphenoxyacetic acid.
             (166) 4-[2-(N-isopropyl-phenylsulfonylamino)-5-methylphenoxymethyl]phenoxyacetic acid.
             (167) 4-[2-(N-isopropyl-phenylsulfonylamino)-5-methylphenoxymethyl]cinnamic acid,
             (168) 4-[2-(N-isopropyl-phenylsulfonylamino)-5-chlorophenoxymethyl]phenoxyacetic acid,
55
             (169) 4-[2-(N-isopropyl-phenylsulfonylamino)-5-chlorophenoxymethyl]cinnamic acid,
             (170) 4-[2-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxy]ethyl]benzoic acid,
             (171) 2-methoxy-4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid.
             (172) 2-hydroxy-4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethylibenzoic acid.
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- (173) 2-hydroxy-4-[2-(N-isopropyl-phenylsulfonylamino)-5-methylphenoxymethyl]b nzoic acid,
- (174) 2-hydroxy-4-[2-(N-isopropyl-phenylsulfonylamino)-5-chlorophenoxymethyl]benzoic acid,
- (175) 4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenylaminomethyl]benzoic acid.
- (176) 4-[N-methyl-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenyl]aminomethyl]benzoic acid,
- (177) 4-[2-[N-(1,3-dihydroxyprop-2-yl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid,
- (178) 4-[2-[N-(1,3-dimethoxyprop-2-yl)-phenylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid,
- (179) 4-[2-(N-isopropyl-1-hexenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
- (180) 4-[2-(N-isopropyl-cyclopentylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
- (181) 4-[2-(N-isopropyl-cyclohexylsulfonylamino)-5-trifluoromethylphenoxymethyllbenzoic acid,
- (182) 4-[2-(N-isopropyl-cyclohexylsulfonylamino)-5-methylphenoxymethyljbenzoic acid.
- (183) 4-[2-(N-isopropyl-isopropylsulfonylamino)-5-trifluoromethylphenoxymethyllbenzoic acid,
- (184) 4-[2-(N-isopropyl-isopropylsulfonylamino)-5-methylphenoxymethyl]benzoic acid,
- (185) 4-[2-(N-isopropyl-isopropylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid.
- (186) 4-[2-(N-isopropyl-cyclopentylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid.
- (187) 4-[2-(N-isopropyl-cyclohexylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid.
- (188) 4-[2-[N-(N,N-dimethylaminocarbonylmethyl)-phenylsulfonylamino]-5-trifluoromethyl-phenoxymethyl]benzoic acid,
- (189) 4-(2-phenylsulfonylamino-5-isopropyl-phenoxymethyl)benzoic acid.
- (190) 4-(2-phenylsulfonylamino-5-ethylphenoxymethyl)benzoic acid,
- (191) 4-(2-phenylsulfonylamino-5hydroxymethylphenoxymethyl)benzoic acid,
- (192) 4-(2-phenylsulfonylaminomethyl-5-chlorophenoxymethyl)benzoic acid,
- (193) 4-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]phenylpropi-

olic acid.

- (194) 4-(2-phenylsulfonylamino-4-chlorophenoxymethyl)benzyl alcohol,
- (195) 4-(2-benzoylamino-5-chlorophenoxymethyl)benzoic acid,
- (196) 4-[2-(N-isopropyl-phenylsulfonylamino)-5-isopropylphenoxymethyl]benzoic acid,
- (197) 4-[2-(N-methyl-phenylsulfonylamino)-5-isopropylphenoxymethyl]benzoic acid,
- (198) 4-(2-(N-isopropyl-phenylsulfonylamino)-5-ethylphenoxymethyl]benzoic acid,
- (199) 4-[2-(N-isopropyl-4-propoxyphenylsulfonylamino)-5-trifluoromethylphenoxymethyllbenzoic acid.
- (200) 4-[2-(N-isopropyl-4-ethylthiophenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
- (201) 4-[2-(N-isopropyl-4-methylthiophenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
- (202) 4-[2-(N-isopropyl-4-butoxyphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
- (203) 4-[2-(N-isopropyl-4-isopropoxyphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
- (204) 4-[2-(N-isobutyl-benzoylamino)-5-chlorophenoxymethyl]benzoic acid,
- (205) 4-[2-(N-isopropyl-benzoylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
- (206) 6-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]-2-naphthalic acid,
- (207) 4-[2-(N-isopropyl-butyrylamino)-5-trif-luoromethylphenoxymethyl]cinnamic acid,
- (208) 4-[2-(N-isopropyl-4-ethoxyphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid.
- (209) 4-[2-(N-isobutyl-4-ethoxyphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid and
- (210) 4-[2-(N-isopropyl-3-ethoxyphenylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid, and methyl esters thereof.
- A compound according to claim 1 which is selected from
 - (1) 4-[2-[2-(4-chlorophenylsulfonylamino)-5-chlorophenyl]-(E)-vinyl]benzoic acid,
 - (2) 4-[2-[2-(4-chlorophenylsulfonylamino)-5-chlorophenyl]-(Z)-vinyl]benzoic acid,
 - (3) 4-[2-[2-(4-chlorophenyl)sulfonylamino-5-chlorophenyl]ethyl]benzoic acid,
 - (4) 4-[2-[2-(4-chlorophenylsulfonylamino)-5-chlorophenyl]ethynyl]benzoic acid,
 - (5) 4-[2-{2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenyl]ethyl]benzoic acid,

- (6) 4-[2-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenyl]-(E)-vinyl]benzoic acid and
- (7) 4-[2-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenyl]-(Z)-vinyl]benzoic acid, and methyl esters thereof.
- A compound according to claim 1 which is selected from
 - 4-[2-(N-isopropyl-2-thienylsulfonylamino)-5chlorophenoxymethyl]benzoic acid,
 - (2) 4-[2-(N-isopropyl-2-thienylsulfonylamino)-5methylphenoxymethylibenzoic acid.
 - (3) 4-[2-(N-isopropyl-2-furanylsulfonylamino)-5-methylphenoxymethyl]benzoic acid.
 - (4) 4-[2-(N-isopropyl-2-furanylsulfonylamino)-5-chlorophenoxymethyl]benzoic acid,
 - (5) 4-[2-(N-propyl-2-furanylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid,
 - (6) 4-[2-(N-propyl-2-furanylsulfonylamino)-5methylphenoxymethyl]benzoic acid,
 - (7) 4-[2-(N-isobutyl-2-furanylsulfonylamino)-5methylphenoxymethyl]benzoic acid,
 - (8) 4-[2-(N-isobutyl-2-furanylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid,
 - (9) 4-[2-[N-(prop-2-enyl)-2-furanylsulfonylamino]-5-methylphenoxymethyl]benzoic acid,
 - (10) 4-[2-[N-(2-methylprop-2-enyl)-2-furanyl-sulfonylamino]-5-methylphenoxymethyl]ben-zoic acid.
 - (11) 4-[2-(N-isobutyl-2-furanylsulfonylamino)-4-methylphenoxymethyl]benzoic acid,
 - (12) 4-[2-(N-isopropyl-2-furanylsulfonylamino)-4-methylphenoxymethyl]benzoic acid,
 - (13) 4-[2-[N-(2-methylprop-2-enyl)-2-furanyl-sulfonylamino]-4-methylphenoxymethyl]ben-zoic acid,
 - (14) 4-[2-(N-isopropyl-2-furanylsulfonylamino)-5-methylphenoxymethyl]cinnamic acid,
 - (15) 4-[2-(N-isopropyl-2-furanylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid,
 (16) 4-[2-(N-isopropyl-2-furanylsulfonylamino)-4-trifluoromethylphenoxymethyl]benzoic acid,
 - (17) 4-[2-(N-isobutyl-2-furanylsulfonylamino)-
 - 4-trifluoromethylphenoxymethyl]benzoic acid,(18) 4-[2-(N-isobutyl-2-furanylsulfonylamino)-
 - 5-chlorophenoxymethyl]benzoic acid, (19) 4-[2-(N-isopropyl-2-furanylsulfonylamino)-5-chlorophenoxymethyl]cinnamic acid,
 - (20) 4-[2-(N-isobutyl-2-furanylsulfonylamino)-5-chlorophenoxymethyllcinnamic acid.
 - (21) 4-[2-(N-isobutyl-2-furanylsulfonylamino)-5-trifluoromethylphenoxymethylphenzoic acid,
 - (22) 4-[2-(N-isobutyl-2-furanylsulfonylamino)-4-chlorophenoxymethyl]benzoic acid,
 - (23) 4-[2-(N-isobutyl-2-furanylsulfonylamino)-

- 4-methylphenoxymethyl]cinnamic acid.
- (24) 4-[2-(N-isopropyl-2-furanylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
- (25) 4-[2-(N-isopropyl-2-thienylsulfonylamino)-5-trifluoromethylphenoxymethyl]benzoic acid,
- (26) 4-[2-[N-(2-hydroxy-2-methylpropyl)-2-thienylsulfonylamino]-5-trifluoromethylphenoxymethyl]benzoic acid.
- (27) 4-[2-(N-isopropyl-2-furoylamino)-5-trifluor-omethylphenoxymethyllbenzoic acid.
- 28) 4-[2-(2-thienylsulfonylamino)-5-chlorobenzoylamino]benzoic acid,
- (29) 4-[2-(N-isopropyl-2-furanylsulfonylamino)-5-methylphenylthiomethyl]benzoic acid,
- (30) 4-[2-(N-isobutyl-2-thienylsulfonylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid.
- (31) 4-[2-(N-isopropyl-2-furoylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid and
- (32) 4-[2-(N-isobutyl-2-furoylamino)-5-trifluoromethylphenoxymethyl]cinnamic acid, and methyl esters thereof.
- A compound according to claim 1 which is selected from
 - (1) 5-[2-(N-isopropyl-phenylsulfonylamino)-5-methylphenoxymethyl]furan-2-carboxylic acid.
 - (2) 6-(2-phenylsulfonylamino-5-chlorophenoxymethyl)nicotinic acid,
 - (3) 5-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]thiophene-2-car-boxylic acid,
 - (4) 5-[2-(N-isopropyl-phenylsulfonylamino)-5-trifluoromethylphenoxymethyl]furan-2-carboxylic acid,
 - (5) 5-[2-(N-isopropyl-phenylsulfonylamino)-5methylphenoxymethyl]thiophene-2-carboxylic acid,
 - (6) 5-[2-(N-isopropyl-phenylsulfonylamino)-5chlorophenoxymethyl]thiophene-2-carboxylic acid.
 - (7) 5-[2-(N-isopropyl-phenylsulfonylamino)-5-chlorophenoxymethyl]furan-2-carboxylic acid and
 - (8) 4-(3-phenylsulfonylamino-5-trifluoromethylpyridine-2-yloxymethyl)benzoic acid, and methyl esters thereof.
- 15. A prostaglandin E₂ antagonist or agonist which comprises the sulfonamide or carboamide derivative of the formula (I) depicted in claim 1 or a nontoxic salt thereof as an active ingredient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/04593

			PCT/JP	97/04593		
	SIFICATION OF SUBJECT MATTER					
	C16 C07C233/25, 233/75, 237/4	2, 311/13, 3	11/21, 311	/17, 311/29,		
	C07D213/76, 213/80, 307/4		· · · · · · · · · · · · · · · · · · ·	/34, 333/40,		
According to International Patent Classification (IPC) or to both national classification and IPC						
B. FIELDS SEARCHED						
Minimum d	ocumentation searched (classification system follower C1 C07D233/25, 233/75, 237/4	by classification syml	bols) 11/21 311	/17. 311/29		
Inc.	C07D213/76, 213/80, 307/4					
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Documental	tion searched other than minimum documentation to the	he extent that such doc	uments are include	d in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS ONLINE						
CAS	ONLINE					
C. DOCUMENTS CONSIDERED TO BE RELEVANT						
Category*	Citation of document, with indication, where a		Relevant to claim No.			
A	JP, 4-308560, A (Eli Lilly			1-15		
	October 30, 1992 (30, 10, 92					
ļ	& EP, 491525, A1 & US, 5397798, A					
A	JP, 2-72150, A (Otsuka Phar	maceutical Fa	actory,	1-15		
	Inc.),					
	March 12, 1990 (12. 03. 90)	(Family: nor	ne)			
A	JP, 59-16871, A (Shionogi &	Co Itd)		1-15		
^	January 28, 1984 (28. 01. 84		none)	1-13		
	dandary 20, 1501 (200 010 01) (Lamber)					
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Furthe	r documents are listed in the continuation of Box C.	See patent fam:	ily annex.			
Special categories of cited documents: T later document published after the international filling date or priority						
A docume	ent defining the general state of the art which is not	date and not in co	nflict with the applica	tion but cited to understand		
	red to be of particular relevance document but published on or after the international filing date	the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be				
L" docume	ent which may throw doubts on priority claim(s) or which is	considered novel or cannot be considered to involve an inventive step				
special	establish the publication date of another citation or other reason (as specified)	when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be				
	ent referring to an oral disclosure, use, exhibition or other	considered to invo	considered to involve an inventive step when the document is			
means 'P' docume	ent published prior to the international filing date but later than	combined with one or more other such documents, such combination being obvious to a person skilled in the art				
the priority date claimed "&" document member of the same patent family						
Date of the actual completion of the international search Date of mailing of the international search report						
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	nese Patent Office	Annua tara dilitet				
Facsimile N	o.	Telephone No.				

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/04593

A. (Continuation) CLASSIFICATION OF SUBJECT MATTER

A61K31/195, 31/24, 31/245, 31/34, 31/38

B. (Continuation) FIELDS SEARCHED

A61K31/195, 31/24, 31/245, 31/34, 31/38

Form PCT/ISA/210 (extra sheet) (July 1992)